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(54) Title: OVARIAN TUMOR-ASSOCIATED SEQUENCES

(57) Abstract: Compositions and methods for the therapy and diagnosis of cancer, such as ovarian cancer, are disclosed. Compositions may comprise one or more ovarian tumor proteins, immunogenic portions thereof, or polynucleotides that encode such portions. Alternatively, a therapeutic composition may comprise an antigen presenting cell that expresses an ovarian tumor protein, or a T cell that is specific for cells expressing such a protein. Such compositions may be used, for example, for the prevention and treatment of diseases such as ovarian cancer. Diagnostic methods based on detecting an ovarian tumor protein, or mRNA encoding such a protein, in a sample are also provided.



**WO 01/51513 A2**

## OVARIAN TUMOR-ASSOCIATED SEQUENCES

### TECHNICAL FIELD

The present invention relates generally to therapy and diagnosis of cancer, such as ovarian cancer. The invention is more specifically related to polypeptides comprising at least a portion of an ovarian tumor protein, and to polynucleotides encoding such polypeptides. Such polypeptides and polynucleotides may be used in vaccines and pharmaceutical compositions for prevention and treatment of cancers such as ovarian cancer, and for the diagnosis and monitoring of such cancers.

### 10 BACKGROUND OF THE INVENTION

Ovarian cancer is a significant health problem for women in the United States and throughout the world. Although advances have been made in detection and therapy of this cancer, no vaccine or other universally successful method for prevention or treatment is currently available. Management of the disease currently relies on a combination of early diagnosis and aggressive treatment, which may include one or more of a variety of treatments such as surgery, radiotherapy, chemotherapy and hormone therapy. The course of treatment for a particular cancer is often selected based on a variety of prognostic parameters, including an analysis of specific tumor markers. However, the use of established markers often leads to a result that is difficult to interpret, and high mortality continues to be observed in many cancer patients.

Immunotherapies have the potential to substantially improve cancer treatment and survival. Such therapies may involve the generation or enhancement of an immune response to an ovarian carcinoma antigen. However, to date, relatively few ovarian carcinoma antigens are known and the generation of an immune response against such antigens has not been shown to be therapeutically beneficial.

Accordingly, there is a need in the art for improved methods for identifying ovarian tumor proteins and for using such proteins in the therapy of ovarian cancer. The present invention fulfills these needs and further provides other related advantages.

## SUMMARY OF THE INVENTION

Briefly stated, the present invention provides compositions and methods for the diagnosis and therapy of cancer, such as ovarian cancer. In one aspect, the present invention provides polypeptides comprising at least a portion of an ovarian tumor protein, or a variant thereof. Certain portions and other variants are immunogenic, such that the ability of the variant to react with antigen-specific antisera is not substantially diminished. Within certain embodiments, the polypeptide comprises a sequence that is encoded by a polynucleotide sequence selected from the group consisting of sequences recited in SEQ ID NOs:1-1502), variants of such sequences and complements of such sequences.

The present invention further provides polynucleotides that encode a polypeptide as described above, or a portion thereof (such as a portion encoding at least 15 amino acid residues of an ovarian tumor protein), expression vectors comprising such polynucleotides and host cells transformed or transfected with such expression vectors.

Within other aspects, the present invention provides pharmaceutical compositions comprising a polypeptide or polynucleotide as described above and a physiologically acceptable carrier.

Within a related aspect of the present invention, vaccines are provided. Such vaccines comprise a polypeptide or polynucleotide as described above and a non-specific immune response enhancer.

The present invention further provides pharmaceutical compositions that comprise: (a) an antibody or antigen-binding fragment thereof that specifically binds to an ovarian tumor protein; and (b) a physiologically acceptable carrier.

Within further aspects, the present invention provides pharmaceutical compositions comprising: (a) an antigen presenting cell that expresses a polypeptide as described above and (b) a pharmaceutically acceptable carrier or excipient. Antigen presenting cells include dendritic cells, macrophages and B cells.

Within related aspects, vaccines are provided that comprise: (a) an antigen presenting cell that expresses a polypeptide as described above and (b) a non-specific immune response enhancer.

The present invention further provides, in other aspects, fusion proteins that comprise at least one polypeptide as described above, as well as polynucleotides encoding such fusion proteins.

Within related aspects, pharmaceutical compositions comprising a fusion  
5 protein, or a polynucleotide encoding a fusion protein, in combination with a physiologically acceptable carrier are provided.

Vaccines are further provided, within other aspects, that comprise a fusion protein or a polynucleotide encoding a fusion protein in combination with a non-specific immune response enhancer.

10 Within further aspects, the present invention provides methods for inhibiting the development of a cancer in a patient, comprising administering to a patient a pharmaceutical composition or vaccine as recited above. The patient may be afflicted with a cancer, in which case the methods provide treatment for the disease, or a patient considered at risk for such a disease may be treated prophylactically.

15 The present invention further provides, within other aspects, methods for removing tumor cells from a biological sample, comprising contacting a biological sample with T cells that specifically react with an ovarian tumor protein, wherein the step of contacting is performed under conditions and for a time sufficient to permit the removal of cells expressing the protein from the sample.

20 Within related aspects, methods are provided for inhibiting the development of a cancer in a patient, comprising administering to a patient a biological sample treated as described above.

Methods are further provided, within other aspects, for stimulating and/or expanding T cells specific for an ovarian tumor protein, comprising contacting T  
25 cells with one or more of: (i) a polypeptide as described above; (ii) a polynucleotide encoding such a polypeptide; and/or (iii) an antigen presenting cell that expresses such a polypeptide; under conditions and for a time sufficient to permit the stimulation and/or expansion of T cells. Isolated T cell populations comprising T cells prepared as described above are also provided.



Within further aspects, the present invention provides methods for inhibiting the development of a cancer in a patient, comprising administering to a patient an effective amount of a T cell population as described above.

The present invention further provides methods for inhibiting the development of a cancer in a patient, comprising the steps of: (a) incubating CD4<sup>+</sup> and/or CD8<sup>+</sup> T cells isolated from a patient with one or more of: (i) a polypeptide comprising at least an immunogenic portion of an ovarian tumor protein; (ii) a polynucleotide encoding such a polypeptide; and (iii) an antigen-presenting cell that expresses such a polypeptide; and (b) administering to the patient an effective amount of the proliferated T cells, and thereby inhibiting the development of a cancer in the patient. Proliferated cells may, but need not, be cloned prior to administration to the patient.

Within further aspects, the present invention provides methods for determining the presence or absence of a cancer in a patient, comprising (a) contacting a biological sample obtained from a patient with a binding agent that binds to a polypeptide as recited above; (b) detecting in the sample an amount of polypeptide that binds to the binding agent; and (c) comparing the amount of polypeptide with a predetermined cut-off value, and therefrom determining the presence or absence of a cancer in the patient. Within preferred embodiments, the binding agent is an antibody, more preferably a monoclonal antibody. The cancer may be ovarian cancer.

The present invention also provides, within other aspects, methods for monitoring the progression of a cancer in a patient. Such methods comprise the steps of: (a) contacting a biological sample obtained from a patient at a first point in time with a binding agent that binds to a polypeptide as recited above; (b) detecting in the sample an amount of polypeptide that binds to the binding agent; (c) repeating steps (a) and (b) using a biological sample obtained from the patient at a subsequent point in time; and (d) comparing the amount of polypeptide detected in step (c) with the amount detected in step (b) and therefrom monitoring the progression of the cancer in the patient.

The present invention further provides, within other aspects, methods for determining the presence or absence of a cancer in a patient, comprising the steps of: (a)

contacting a biological sample obtained from a patient with an oligonucleotide that hybridizes to a polynucleotide that encodes an ovarian tumor protein; (b) detecting in the sample a level of a polynucleotide, preferably mRNA, that hybridizes to the oligonucleotide; and (c) comparing the level of polynucleotide that hybridizes to the oligonucleotide with a predetermined cut-off value, and therefrom determining the presence or absence of a cancer in the patient. Within certain embodiments, the amount of mRNA is detected via polymerase chain reaction using, for example, at least one oligonucleotide primer that hybridizes to a polynucleotide encoding a polypeptide as recited above, or a complement of such a polynucleotide. Within other embodiments, the amount of mRNA is detected using a hybridization technique, employing an oligonucleotide probe that hybridizes to a polynucleotide that encodes a polypeptide as recited above, or a complement of such a polynucleotide.

In related aspects, methods are provided for monitoring the progression of a cancer in a patient, comprising the steps of: (a) contacting a biological sample obtained from a patient with an oligonucleotide that hybridizes to a polynucleotide that encodes an ovarian tumor protein; (b) detecting in the sample an amount of a polynucleotide that hybridizes to the oligonucleotide; (c) repeating steps (a) and (b) using a biological sample obtained from the patient at a subsequent point in time; and (d) comparing the amount of polynucleotide detected in step (c) with the amount detected in step (b) and therefrom monitoring the progression of the cancer in the patient.

Within further aspects, the present invention provides antibodies, such as monoclonal antibodies, that bind to a polypeptide as described above, as well as diagnostic kits comprising such antibodies. Diagnostic kits comprising one or more oligonucleotide probes or primers as described above are also provided.

These and other aspects of the present invention will become apparent upon reference to the following detailed description. All references disclosed herein are hereby incorporated by reference in their entirety as if each was incorporated individually.

## DETAILED DESCRIPTION OF THE INVENTION

As noted above, the present invention is generally directed to compositions and methods for the therapy and diagnosis of cancer, such as ovarian cancer. The compositions described herein may comprise ovarian tumor polypeptides, polynucleotides encoding such polypeptides, binding agents such as antibodies, antigen presenting cells (APCs) and/or immune system cells (*e.g.*, T cells). Polypeptides of the present invention generally comprise at least a portion (such as an immunogenic portion) of an ovarian tumor protein or a variant thereof. An "ovarian tumor protein" is a protein that is encoded by an ovarian tumor polynucleotide, as provided herein. An "ovarian tumor polynucleotide" is a polynucleotide that comprises, or is complementary to, a cDNA sequence that is present at a greater level in cDNA from ovarian tumor cells than in cDNA from non-ovarian tissue. Preferably, the level in ovarian tumor cDNA is at least two fold, more preferably at least five fold, greater than the level of expression in a non-ovarian tissue. Certain ovarian tumor proteins are tumor-specific (*i.e.*, are expressed at higher levels in ovarian tumors than in normal ovarian cells). Such proteins may be used as markers to detect or monitor ovarian cancer in patients. Other ovarian tumor proteins are present at comparable levels in both normal ovarian cells and ovarian tumor cells. These proteins may be ovary-tissue specific. Antibodies are generally immune system proteins, or antigen-binding fragments thereof, that are capable of binding to a polypeptide as described above. Antigen presenting cells include dendritic cells and macrophages that express a polypeptide as described above. T cells that may be employed within such compositions are generally T cells that are specific for a polypeptide as described above.

The present invention is based on the discovery of previously unknown human ovarian tumor proteins. Partial sequences of polynucleotides encoding specific tumor proteins are provided in SEQ ID NOs:1-1502.

## OVARIAN TUMOR POLYNUCLEOTIDES

Any polynucleotide that encodes an ovarian tumor protein or a portion or other variant thereof as described herein is encompassed by the present invention. Preferred polynucleotides comprise at least 15 consecutive nucleotides, preferably at

least 30 consecutive nucleotides and more preferably at least 45 consecutive nucleotides, that encode a portion of an ovarian tumor protein. More preferably, a polynucleotide encodes an immunogenic portion of an ovarian tumor protein. Polynucleotides complementary to any such sequences are also encompassed by the present invention. Polynucleotides may be single-stranded (coding or antisense) or double-stranded, and may be DNA (genomic, cDNA or synthetic) or RNA molecules. RNA molecules include HnRNA molecules, which contain introns and correspond to a DNA molecule in a one-to-one manner, and mRNA molecules, which do not contain introns. Additional coding or non-coding sequences may, but need not, be present within a polynucleotide of the present invention, and a polynucleotide may, but need not, be linked to other molecules and/or support materials.

Polynucleotides may comprise a native sequence (*i.e.*, an endogenous sequence that encodes an ovarian tumor protein or a portion thereof) or may comprise a variant of such a sequence. Polynucleotide variants may contain one or more substitutions, additions, deletions and/or insertions such that the immunogenicity of the encoded polypeptide is not diminished, relative to a native tumor protein. The effect on the immunogenicity of the encoded polypeptide may generally be assessed as described herein. Variants preferably exhibit at least about 70% identity, more preferably at least about 80% identity and most preferably at least about 90% identity to a polynucleotide sequence that encodes a native ovarian tumor protein or a portion thereof.

The percent identity for two polynucleotide or polypeptide sequences may be readily determined by comparing sequences using computer algorithms well known to those of ordinary skill in the art, such as Megalign, using default parameters. Comparisons between two sequences are typically performed by comparing the sequences over a comparison window to identify and compare local regions of sequence similarity. A "comparison window" as used herein, refers to a segment of at least about 20 contiguous positions, usually 30 to about 75, or 40 to about 50, in which a sequence may be compared to a reference sequence of the same number of contiguous positions after the two sequences are optimally aligned. Optimal alignment of sequences for comparison may be conducted, for example, using the Megalign program in the Lasergene suite of bioinformatics software (DNASTAR, Inc., Madison, WI), using

default parameters. Preferably, the percentage of sequence identity is determined by comparing two optimally aligned sequences over a window of comparison of at least 20 positions, wherein the portion of the polynucleotide or polypeptide sequence in the window may comprise additions or deletions (*i.e.*, gaps) of 20 % or less, usually 5 to 15  
5 %, or 10 to 12%, relative to the reference sequence (which does not contain additions or deletions). The percent identity may be calculated by determining the number of positions at which the identical nucleic acid bases or amino acid residue occurs in both sequences to yield the number of matched positions, dividing the number of matched positions by the total number of positions in the reference sequence (*i.e.*, the window  
10 size) and multiplying the results by 100 to yield the percentage of sequence identity.

Variants may also, or alternatively, be substantially homologous to a native gene, or a portion or complement thereof. Such polynucleotide variants are capable of hybridizing under moderately stringent conditions to a naturally occurring DNA sequence encoding a native ovarian tumor protein (or a complementary sequence).  
15 Suitable moderately stringent conditions include prewashing in a solution of 5 X SSC, 0.5% SDS, 1.0 mM EDTA (pH 8.0); hybridizing at 50°C-65°C, 5 X SSC, overnight; followed by washing twice at 65°C for 20 minutes with each of 2X, 0.5X and 0.2X SSC containing 0.1% SDS.

It will be appreciated by those of ordinary skill in the art that, as a result  
20 of the degeneracy of the genetic code, there are many nucleotide sequences that encode a polypeptide as described herein. Some of these polynucleotides bear minimal homology to the nucleotide sequence of any native gene. Nonetheless, polynucleotides that vary due to differences in codon usage are specifically contemplated by the present invention. Further, alleles of the genes comprising the polynucleotide sequences  
25 provided herein are within the scope of the present invention. Alleles are endogenous genes that are altered as a result of one or more mutations, such as deletions, additions and/or substitutions of nucleotides. The resulting mRNA and protein may, but need not, have an altered structure or function. Alleles may be identified using standard techniques (such as hybridization, amplification and/or database sequence comparison).

30 Polynucleotides may be prepared using any of a variety of techniques. For example, a polynucleotide may be identified using a PCR-based cDNA subtraction

approach. Briefly, such screens may be performed using the PCR-Select cDNA Subtraction method (Clontech). The tester cDNA library may be obtained using pooled mRNA from multiple ovarian metastatic tumors, and the driver library may be obtained from pooled mRNA from multiple non-ovarian normal tissues. Alternatively, a  
5 microarray of cDNAs may be screened for tumor-associated expression. Such screens may be performed using a Synteni microarray (Palo Alto, CA) according to the manufacturer's instructions (and essentially as described by Schena et al., *Proc. Natl. Acad. Sci. USA* 93:10614-10619, 1996 and Heller et al., *Proc. Natl. Acad. Sci. USA* 94:2150-2155, 1997). Within yet another screen, polynucleotides may be amplified  
10 from cDNA prepared from cells expressing the proteins described herein, such as ovarian tumor cells. Such polynucleotides may be amplified via polymerase chain reaction (PCR). For this approach, sequence-specific primers may be designed based on the sequences provided herein, and may be purchased or synthesized.

An amplified portion may be used to isolate a full length gene from a  
15 suitable library (e.g., an ovarian tumor cDNA library) using well known techniques. Within such techniques, a library (cDNA or genomic) is screened using one or more polynucleotide probes or primers suitable for amplification. Preferably, a library is size-selected to include larger molecules. Random primed libraries may also be preferred for identifying 5' and upstream regions of genes. Genomic libraries are preferred for  
20 obtaining introns and extending 5' sequences.

For hybridization techniques, a partial sequence may be labeled (e.g., by nick-translation or end-labeling with  $^{32}\text{P}$ ) using well known techniques. A bacterial or bacteriophage library is then screened by hybridizing filters containing denatured bacterial colonies (or lawns containing phage plaques) with the labeled probe (see  
25 Sambrook et al., *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Laboratories, Cold Spring Harbor, NY, 1989). Hybridizing colonies or plaques are selected and expanded, and the DNA is isolated for further analysis. cDNA clones may be analyzed to determine the amount of additional sequence by, for example, PCR using a primer from the partial sequence and a primer from the vector. Restriction maps and  
30 partial sequences may be generated to identify one or more overlapping clones. The complete sequence may then be determined using standard techniques, which may

involve generating a series of deletion clones. The resulting overlapping sequences are then assembled into a single contiguous sequence. A full length cDNA molecule can be generated by ligating suitable fragments, using well known techniques.

Alternatively, there are numerous amplification techniques for obtaining  
5 a full length coding sequence from a partial cDNA sequence. Within such techniques, amplification is generally performed via PCR. Any of a variety of commercially available kits may be used to perform the amplification step. Primers may be designed using, for example, software well known in the art. Primers are preferably 22-30 nucleotides in length, have a GC content of at least 50% and anneal to the target  
10 sequence at temperatures of about 68°C to 72°C. The amplified region may be sequenced as described above, and overlapping sequences assembled into a contiguous sequence.

One such amplification technique is inverse PCR (*see* Triglia et al., *Nucl. Acids Res.* 16:8186, 1988), which uses restriction enzymes to generate a fragment in the  
15 known region of the gene. The fragment is then circularized by intramolecular ligation and used as a template for PCR with divergent primers derived from the known region. Within an alternative approach, sequences adjacent to a partial sequence may be retrieved by amplification with a primer to a linker sequence and a primer specific to a known region. The amplified sequences are typically subjected to a second round of  
20 amplification with the same linker primer and a second primer specific to the known region. A variation on this procedure, which employs two primers that initiate extension in opposite directions from the known sequence, is described in WO 96/38591. Another such technique is known as "rapid amplification of cDNA ends" or RACE. This technique involves the use of an internal primer and an external primer,  
25 which hybridizes to a polyA region or vector sequence, to identify sequences that are 5' and 3' of a known sequence. Additional techniques include capture PCR (Lagerstrom et al., *PCR Methods Applic.* 1:111-19, 1991) and walking PCR (Parker et al., *Nucl. Acids Res.* 19:3055-60, 1991). Other methods employing amplification may also be employed to obtain a full length cDNA sequence.

30 In certain instances, it is possible to obtain a full length cDNA sequence by analysis of sequences provided in an expressed sequence tag (EST) database, such as

that available from GenBank. Searches for overlapping ESTs may generally be performed using well known programs (*e.g.*, NCBI BLAST searches), and such ESTs may be used to generate a contiguous full length sequence.

Certain nucleic acid sequences of cDNA molecules encoding portions of ovarian tumor proteins are provided in SEQ ID NOs:1-1502. These polynucleotides were isolated by PCR-based subtraction. This technique serves to normalize differentially expressed cDNAs, facilitating the recovery of rare transcripts, and also has the advantage of permitting enrichment of cDNAs with small amounts of polyA RNA material and without multiple rounds of hybridization. In one subtraction, a pool of four ovary metastatic omentum mRNAs was used to generate the tester library. This library was subtracted with driver mRNA, pooled from brain, pancreas, bone marrow, lung, heart, kidney, liver and trachea. In a second subtraction, the tester library was generated from a pool of primary ovary tumor mRNAs, including an endometroid adenocarcinoma, a germ cell tumor, a papillary serous adenocarcinoma and a clear cell carcinoma, and subtracted with the driver library discussed above. PCR-amplified pools were generated from the subtracted libraries and clones corresponding to SEQ ID NOs:1-1502 were sequenced.

Polynucleotide variants may generally be prepared by any method known in the art, including chemical synthesis by, for example, solid phase phosphoramidite chemical synthesis. Modifications in a polynucleotide sequence may also be introduced using standard mutagenesis techniques, such as oligonucleotide-directed site-specific mutagenesis (*see* Adelman et al., *DNA* 2:183, 1983). Alternatively, RNA molecules may be generated by *in vitro* or *in vivo* transcription of DNA sequences encoding an ovarian tumor protein, or portion thereof, provided that the DNA is incorporated into a vector with a suitable RNA polymerase promoter (such as T7 or SP6). Certain portions may be used to prepare an encoded polypeptide, as described herein. In addition, or alternatively, a portion may be administered to a patient such that the encoded polypeptide is generated *in vivo* (*e.g.*, by transfecting antigen-presenting cells, such as dendritic cells, with a cDNA construct encoding an ovarian tumor polypeptide, and administering the transfected cells to the patient).



A portion of a sequence complementary to a coding sequence (*i.e.*, an antisense polynucleotide) may also be used as a probe or to modulate gene expression. cDNA constructs that can be transcribed into antisense RNA may also be introduced into cells or tissues to facilitate the production of antisense RNA. An antisense polynucleotide may be used, as described herein, to inhibit expression of a tumor protein. Antisense technology can be used to control gene expression through triple-helix formation, which compromises the ability of the double helix to open sufficiently for the binding of polymerases, transcription factors or regulatory molecules (*see* Gee et al., *In* Huber and Carr, *Molecular and Immunologic Approaches*, Futura Publishing Co. (Mt. Kisco, NY; 1994)). Alternatively, an antisense molecule may be designed to hybridize with a control region of a gene (*e.g.*, promoter, enhancer or transcription initiation site), and block transcription of the gene; or to block translation by inhibiting binding of a transcript to ribosomes.

A portion of a coding sequence or of a complementary sequence may also be designed as a probe or primer to detect gene expression. Probes may be labeled with a variety of reporter groups, such as radionuclides and enzymes, and are preferably at least 10 nucleotides in length, more preferably at least 20 nucleotides in length and still more preferably at least 30 nucleotides in length. Primers, as noted above, are preferably 22-30 nucleotides in length.

Any polynucleotide may be further modified to increase stability *in vivo*. Possible modifications include, but are not limited to, the addition of flanking sequences at the 5' and/or 3' ends; the use of phosphorothioate or 2' O-methyl rather than phosphodiesterase linkages in the backbone; and/or the inclusion of nontraditional bases such as inosine, queosine and wybutosine, as well as acetyl-, methyl-, thio- and other modified forms of adenine, cytidine, guanine, thymine and uridine.

Nucleotide sequences as described herein may be joined to a variety of other nucleotide sequences using established recombinant DNA techniques. For example, a polynucleotide may be cloned into any of a variety of cloning vectors, including plasmids, phagemids, lambda phage derivatives and cosmids. Vectors of particular interest include expression vectors, replication vectors, probe generation vectors and sequencing vectors. In general, a vector will contain an origin of replication

functional in at least one organism, convenient restriction endonuclease sites and one or more selectable markers. Other elements will depend upon the desired use, and will be apparent to those of ordinary skill in the art.

Within certain embodiments, polynucleotides may be formulated so as to permit entry into a cell of a mammal, and expression therein. Such formulations are particularly useful for therapeutic purposes, as described below. Those of ordinary skill in the art will appreciate that there are many ways to achieve expression of a polynucleotide in a target cell, and any suitable method may be employed. For example, a polynucleotide may be incorporated into a viral vector such as, but not limited to, adenovirus, adeno-associated virus, retrovirus, or vaccinia or other pox virus (*e.g.*, avian pox virus). The polynucleotides may also be administered as naked plasmid vectors. Techniques for incorporating DNA into such vectors are well known to those of ordinary skill in the art. A retroviral vector may additionally transfer or incorporate a gene for a selectable marker (to aid in the identification or selection of transduced cells) and/or a targeting moiety, such as a gene that encodes a ligand for a receptor on a specific target cell, to render the vector target specific. Targeting may also be accomplished using an antibody, by methods known to those of ordinary skill in the art.

Other formulations for therapeutic purposes include colloidal dispersion systems, such as macromolecule complexes, nanocapsules, microspheres, beads, and lipid-based systems including oil-in-water emulsions, micelles, mixed micelles, and liposomes. A preferred colloidal system for use as a delivery vehicle *in vitro* and *in vivo* is a liposome (*i.e.*, an artificial membrane vesicle). The preparation and use of such systems is well known in the art.

## OVARIAN TUMOR POLYPEPTIDES

Within the context of the present invention, polypeptides may comprise at least an immunogenic portion of an ovarian tumor protein or a variant thereof, as described herein. As noted above, an "ovarian tumor protein" is a protein that is expressed by ovarian tumor cells. Proteins that are ovarian tumor proteins may also react detectably within an immunoassay (such as an ELISA) with antisera from a patient with ovarian cancer. Polypeptides as described herein may be of any length. Additional

sequences derived from the native protein and/or heterologous sequences may be present, and such sequences may (but need not) possess further immunogenic or antigenic properties.

An "immunogenic portion," as used herein is a portion of a protein that is recognized (*i.e.*, specifically bound) by a B-cell and/or T-cell surface antigen receptor. Such immunogenic portions generally comprise at least 5 amino acid residues, more preferably at least 10, and still more preferably at least 20 amino acid residues of an ovarian tumor protein or a variant thereof. Certain preferred immunogenic portions include peptides in which an N-terminal leader sequence and/or transmembrane domain have been deleted. Other preferred immunogenic portions may contain a small N- and/or C-terminal deletion (*e.g.*, 1-30 amino acids, preferably 5-15 amino acids), relative to the mature protein.

Immunogenic portions may generally be identified using well known techniques, such as those summarized in Paul, *Fundamental Immunology*, 3rd ed., 243-247 (Raven Press, 1993) and references cited therein. Such techniques include screening polypeptides for the ability to react with antigen-specific antibodies, antisera and/or T-cell lines or clones. As used herein, antisera and antibodies are "antigen-specific" if they specifically bind to an antigen (*i.e.*, they react with the protein in an ELISA or other immunoassay, and do not react detectably with unrelated proteins). Such antisera and antibodies may be prepared as described herein, and using well known techniques. An immunogenic portion of a native ovarian tumor protein is a portion that reacts with such antisera and/or T-cells at a level that is not substantially less than the reactivity of the full length polypeptide (*e.g.*, in an ELISA and/or T-cell reactivity assay). Such immunogenic portions may react within such assays at a level that is similar to or greater than the reactivity of the full length polypeptide. Such screens may generally be performed using methods well known to those of ordinary skill in the art, such as those described in Harlow and Lane, *Antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratory, 1988. For example, a polypeptide may be immobilized on a solid support and contacted with patient sera to allow binding of antibodies within the sera to the immobilized polypeptide. Unbound sera may then be removed and bound antibodies detected using, for example, <sup>125</sup>I-labeled Protein A.

As noted above, a composition may comprise a variant of a native ovarian tumor protein. A polypeptide "variant," as used herein, is a polypeptide that differs from a native ovarian tumor protein in one or more substitutions, deletions, additions and/or insertions, such that the immunogenicity of the polypeptide is not substantially diminished. In other words, the ability of a variant to react with antigen-specific antisera may be enhanced or unchanged, relative to the native protein, or may be diminished by less than 50%, and preferably less than 20%, relative to the native protein. Such variants may generally be identified by modifying one of the above polypeptide sequences and evaluating the reactivity of the modified polypeptide with antigen-specific antibodies or antisera as described herein. Preferred variants include those in which one or more portions, such as an N-terminal leader sequence or transmembrane domain, have been removed. Other preferred variants include variants in which a small portion (*e.g.*, 1-30 amino acids, preferably 5-15 amino acids) has been removed from the N- and/or C-terminal of the mature protein.

Polypeptide variants preferably exhibit at least about 70%, more preferably at least about 90% and most preferably at least about 95% identity to the native polypeptide. The percent identity may be determined as described above. Preferably, a variant contains conservative substitutions. A "conservative substitution" is one in which an amino acid is substituted for another amino acid that has similar properties, such that one skilled in the art of peptide chemistry would expect the secondary structure and hydrophobic nature of the polypeptide to be substantially unchanged. Amino acid substitutions may generally be made on the basis of similarity in polarity, charge, solubility, hydrophobicity, hydrophilicity and/or the amphipathic nature of the residues. For example, negatively charged amino acids include aspartic acid and glutamic acid; positively charged amino acids include lysine and arginine; and amino acids with uncharged polar head groups having similar hydrophilicity values include leucine, isoleucine and valine; glycine and alanine; asparagine and glutamine; and serine, threonine, phenylalanine and tyrosine. Other groups of amino acids that may represent conservative changes include: (1) ala, pro, gly, glu, asp, gln, asn, ser, thr; (2) cys, ser, tyr, thr; (3) val, ile, leu, met, ala, phe; (4) lys, arg, his; and (5) phe, tyr, trp, his. A variant may also, or alternatively, contain nonconservative changes. In a

preferred embodiment, variant polypeptides differ from a native sequence by substitution, deletion or addition of five amino acids or fewer. Variants may also (or alternatively) be modified by, for example, the deletion or addition of amino acids that have minimal influence on the immunogenicity, secondary structure and hydrophobic nature of the polypeptide.

As noted above, polypeptides may comprise a signal (or leader) sequence at the N-terminal end of the protein, which co-translationally or post-translationally directs transfer of the protein. The polypeptide may also be conjugated to a linker or other sequence for ease of synthesis, purification or identification of the polypeptide (*e.g.*, poly-His), or to enhance binding of the polypeptide to a solid support. For example, a polypeptide may be conjugated to an immunoglobulin Fc region.

Polypeptides may be prepared using any of a variety of well known techniques. Recombinant polypeptides encoded by DNA sequences as described above may be readily prepared from the DNA sequences using any of a variety of expression vectors known to those of ordinary skill in the art. Expression may be achieved in any appropriate host cell that has been transformed or transfected with an expression vector containing a DNA molecule that encodes a recombinant polypeptide. Suitable host cells include prokaryotes, yeast and higher eukaryotic cells, such as mammalian or plant cells. Preferably, the host cells employed are *E. coli*, yeast or a mammalian cell line such as COS or CHO. Supernatants from suitable host/vector systems which secrete recombinant protein or polypeptide into culture media may be first concentrated using a commercially available filter. Following concentration, the concentrate may be applied to a suitable purification matrix such as an affinity matrix or an ion exchange resin. Finally, one or more reverse phase HPLC steps can be employed to further purify a recombinant polypeptide.

Portions and other variants having less than about 100 amino acids, and generally less than about 50 amino acids, may also be generated by synthetic means, using techniques well known to those of ordinary skill in the art. For example, such polypeptides may be synthesized using any of the commercially available solid-phase techniques, such as the Merrifield solid-phase synthesis method, where amino acids are sequentially added to a growing amino acid chain. *See Merrifield, J. Am. Chem. Soc.*

85:2149-2146, 1963. Equipment for automated synthesis of polypeptides is commercially available from suppliers such as Perkin Elmer/Applied BioSystems Division (Foster City, CA), and may be operated according to the manufacturer's instructions.

5                   Within certain specific embodiments, a polypeptide may be a fusion protein that comprises multiple polypeptides as described herein, or that comprises at least one polypeptide as described herein and an unrelated sequence, such as a known tumor protein. A fusion partner may, for example, assist in providing T helper epitopes (an immunological fusion partner), preferably T helper epitopes recognized by humans,  
10 or may assist in expressing the protein (an expression enhancer) at higher yields than the native recombinant protein. Certain preferred fusion partners are both immunological and expression enhancing fusion partners. Other fusion partners may be selected so as to increase the solubility of the protein or to enable the protein to be targeted to desired intracellular compartments. Still further fusion partners include affinity tags, which  
15 facilitate purification of the protein.

                  Fusion proteins may generally be prepared using standard techniques, including chemical conjugation. Preferably, a fusion protein is expressed as a recombinant protein, allowing the production of increased levels, relative to a non-fused protein, in an expression system. Briefly, DNA sequences encoding the polypeptide  
20 components may be assembled separately, and ligated into an appropriate expression vector. The 3' end of the DNA sequence encoding one polypeptide component is ligated, with or without a peptide linker, to the 5' end of a DNA sequence encoding the second polypeptide component so that the reading frames of the sequences are in phase. This permits translation into a single fusion protein that retains the biological activity of  
25 both component polypeptides.

                  A peptide linker sequence may be employed to separate the first and second polypeptide components by a distance sufficient to ensure that each polypeptide folds into its secondary and tertiary structures. Such a peptide linker sequence is incorporated into the fusion protein using standard techniques well known in the art.  
30 Suitable peptide linker sequences may be chosen based on the following factors: (1) their ability to adopt a flexible extended conformation; (2) their inability to adopt a

secondary structure that could interact with functional epitopes on the first and second polypeptides; and (3) the lack of hydrophobic or charged residues that might react with the polypeptide functional epitopes. Preferred peptide linker sequences contain Gly, Asn and Ser residues. Other near neutral amino acids, such as Thr and Ala may also be used in the linker sequence. Amino acid sequences which may be usefully employed as linkers include those disclosed in Maratea et al., *Gene* 40:39-46, 1985; Murphy et al., *Proc. Natl. Acad. Sci. USA* 83:8258-8262, 1986; U.S. Patent No. 4,935,233 and U.S. Patent No. 4,751,180. The linker sequence may generally be from 1 to about 50 amino acids in length. Linker sequences are not required when the first and second polypeptides have non-essential N-terminal amino acid regions that can be used to separate the functional domains and prevent steric interference.

The ligated DNA sequences are operably linked to suitable transcriptional or translational regulatory elements. The regulatory elements responsible for expression of DNA are located only 5' to the DNA sequence encoding the first polypeptides. Similarly, stop codons required to end translation and transcription termination signals are only present 3' to the DNA sequence encoding the second polypeptide.

Also provided are fusion proteins that comprise a polypeptide as described herein together with an unrelated immunogenic protein. Preferably, the immunogenic protein is capable of eliciting a recall response. Examples of such proteins include tetanus, tuberculosis and hepatitis proteins (*see, e.g.,* Stoute et al., *New Engl. J. Med.* 336:86-91, 1997).

Within preferred embodiments, an immunological fusion partner is derived from protein D, a surface protein of the gram-negative bacterium *Haemophilus influenza B* (WO 91/18926). Preferably, a protein D derivative comprises approximately the first third of the protein (*e.g.,* the first N-terminal 100-110 amino acids), and a protein D derivative may be lipidated. Within certain preferred embodiments, the first 109 residues of a Lipoprotein D fusion partner is included on the N-terminus to provide the polypeptide with additional exogenous T-cell epitopes and to increase the expression level in *E. coli* (thus functioning as an expression enhancer). The lipid tail ensures optimal presentation of the antigen to antigen present cells. Other

fusion partners include the non-structural protein from influenzae virus, NS1 (hemagglutinin). Typically, the N-terminal 81 amino acids are used, although different fragments that include T-helper epitopes may be used.

In another embodiment, the immunological fusion partner is the protein known as LYTA, or a portion thereof (preferably a C-terminal portion). LYTA is derived from *Streptococcus pneumoniae*, which synthesizes an N-acetyl-L-alanine amidase known as amidase LYTA (encoded by the *LytA* gene; *Gene* 43:265-292, 1986). LYTA is an autolysin that specifically degrades certain bonds in the peptidoglycan backbone. The C-terminal domain of the LYTA protein is responsible for the affinity to the choline or to some choline analogues such as DEAE. This property has been exploited for the development of *E. coli* C-LYTA expressing plasmids useful for expression of fusion proteins. Purification of hybrid proteins containing the C-LYTA fragment at the amino terminus has been described (*see Biotechnology* 10:795-798, 1992). Within a preferred embodiment, a repeat portion of LYTA may be incorporated into a fusion protein. A repeat portion is found in the C-terminal region starting at residue 178. A particularly preferred repeat portion incorporates residues 188-305.

In general, polypeptides (including fusion proteins) and polynucleotides as described herein are isolated. An "isolated" polypeptide or polynucleotide is one that is removed from its original environment. For example, a naturally-occurring protein is isolated if it is separated from some or all of the coexisting materials in the natural system. Preferably, such polypeptides are at least about 90% pure, more preferably at least about 95% pure and most preferably at least about 99% pure. A polynucleotide is considered to be isolated if, for example, it is cloned into a vector that is not a part of the natural environment.

25

#### BINDING AGENTS

The present invention further provides agents, such as antibodies and antigen-binding fragments thereof, that specifically bind to an ovarian tumor protein. As used herein, an antibody, or antigen-binding fragment thereof, is said to "specifically bind" to an ovarian tumor protein if it reacts at a detectable level (within, for example, an ELISA) with an ovarian tumor protein, and does not react detectably with unrelated

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proteins under similar conditions. As used herein, "binding" refers to a noncovalent association between two separate molecules such that a complex is formed. The ability to bind may be evaluated by, for example, determining a binding constant for the formation of the complex. The binding constant is the value obtained when the concentration of the complex is divided by the product of the component concentrations. In general, two compounds are said to "bind," in the context of the present invention, when the binding constant for complex formation exceeds about  $10^3$  L/mol. The binding constant may be determined using methods well known in the art.

Binding agents may be further capable of differentiating between patients with and without a cancer, such as ovarian cancer, using the representative assays provided herein. In other words, antibodies or other binding agents that bind to an ovarian tumor protein will generate a signal indicating the presence of a cancer in at least about 20% of patients with the disease, and will generate a negative signal indicating the absence of the disease in at least about 90% of individuals without the cancer. To determine whether a binding agent satisfies this requirement, biological samples (*e.g.*, blood, sera, leukophoresis, urine and/or tumor biopsies) from patients with and without a cancer (as determined using standard clinical tests) may be assayed as described herein for the presence of polypeptides that bind to the binding agent. It will be apparent that a statistically significant number of samples with and without the disease should be assayed. Each binding agent should satisfy the above criteria; however, those of ordinary skill in the art will recognize that binding agents may be used in combination to improve sensitivity.

Any agent that satisfies the above requirements may be a binding agent. For example, a binding agent may be a ribosome, with or without a peptide component, an RNA molecule or a polypeptide. In a preferred embodiment, a binding agent is an antibody or an antigen-binding fragment thereof. Antibodies may be prepared by any of a variety of techniques known to those of ordinary skill in the art. *See, e.g.*, Harlow and Lane, *Antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratory, 1988. In general, antibodies can be produced by cell culture techniques, including the generation of monoclonal antibodies as described herein, or via transfection of antibody genes into suitable bacterial or mammalian cell hosts, in order to allow for the production of

recombinant antibodies. In one technique, an immunogen comprising the polypeptide is initially injected into any of a wide variety of mammals (*e.g.*, mice, rats, rabbits, sheep or goats). In this step, the polypeptides of this invention may serve as the immunogen without modification. Alternatively, particularly for relatively short polypeptides, a superior immune response may be elicited if the polypeptide is joined to a carrier protein, such as bovine serum albumin or keyhole limpet hemocyanin. The immunogen is injected into the animal host, preferably according to a predetermined schedule incorporating one or more booster immunizations, and the animals are bled periodically. Polyclonal antibodies specific for the polypeptide may then be purified from such antisera by, for example, affinity chromatography using the polypeptide coupled to a suitable solid support.

Monoclonal antibodies specific for an antigenic polypeptide of interest may be prepared, for example, using the technique of Kohler and Milstein, *Eur. J. Immunol.* 6:511-519, 1976, and improvements thereto. Briefly, these methods involve the preparation of immortal cell lines capable of producing antibodies having the desired specificity (*i.e.*, reactivity with the polypeptide of interest). Such cell lines may be produced, for example, from spleen cells obtained from an animal immunized as described above. The spleen cells are then immortalized by, for example, fusion with a myeloma cell fusion partner, preferably one that is syngeneic with the immunized animal. A variety of fusion techniques may be employed. For example, the spleen cells and myeloma cells may be combined with a nonionic detergent for a few minutes and then plated at low density on a selective medium that supports the growth of hybrid cells, but not myeloma cells. A preferred selection technique uses HAT (hypoxanthine, aminopterin, thymidine) selection. After a sufficient time, usually about 1 to 2 weeks, colonies of hybrids are observed. Single colonies are selected and their culture supernatants tested for binding activity against the polypeptide. Hybridomas having high reactivity and specificity are preferred.

Monoclonal antibodies may be isolated from the supernatants of growing hybridoma colonies. In addition, various techniques may be employed to enhance the yield, such as injection of the hybridoma cell line into the peritoneal cavity of a suitable vertebrate host, such as a mouse. Monoclonal antibodies may then be harvested from

the ascites fluid or the blood. Contaminants may be removed from the antibodies by conventional techniques, such as chromatography, gel filtration, precipitation, and extraction. The polypeptides of this invention may be used in the purification process in, for example, an affinity chromatography step.

5                Within certain embodiments, the use of antigen-binding fragments of antibodies may be preferred. Such fragments include Fab fragments, which may be prepared using standard techniques. Briefly, immunoglobulins may be purified from rabbit serum by affinity chromatography on Protein A bead columns (Harlow and Lane, *Antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratory, 1988) and digested  
10 by papain to yield Fab and Fc fragments. The Fab and Fc fragments may be separated by affinity chromatography on protein A bead columns.

Monoclonal antibodies of the present invention may be coupled to one or more therapeutic agents. Suitable agents in this regard include radionuclides, differentiation inducers, drugs, toxins, and derivatives thereof. Preferred radionuclides  
15 include  $^{90}\text{Y}$ ,  $^{123}\text{I}$ ,  $^{125}\text{I}$ ,  $^{131}\text{I}$ ,  $^{186}\text{Re}$ ,  $^{188}\text{Re}$ ,  $^{211}\text{At}$ , and  $^{212}\text{Bi}$ . Preferred drugs include methotrexate, and pyrimidine and purine analogs. Preferred differentiation inducers include phorbol esters and butyric acid. Preferred toxins include ricin, abrin, diphtheria toxin, cholera toxin, gelonin, *Pseudomonas* exotoxin, *Shigella* toxin, and pokeweed antiviral protein.

20                A therapeutic agent may be coupled (*e.g.*, covalently bonded) to a suitable monoclonal antibody either directly or indirectly (*e.g.*, via a linker group). A direct reaction between an agent and an antibody is possible when each possesses a substituent capable of reacting with the other. For example, a nucleophilic group, such as an amino or sulfhydryl group, on one may be capable of reacting with a carbonyl-  
25 containing group, such as an anhydride or an acid halide, or with an alkyl group containing a good leaving group (*e.g.*, a halide) on the other.

Alternatively, it may be desirable to couple a therapeutic agent and an antibody via a linker group. A linker group can function as a spacer to distance an antibody from an agent in order to avoid interference with binding capabilities. A linker  
30 group can also serve to increase the chemical reactivity of a substituent on an agent or an antibody, and thus increase the coupling efficiency. An increase in chemical

reactivity may also facilitate the use of agents, or functional groups on agents, which otherwise would not be possible.

It will be evident to those skilled in the art that a variety of bifunctional or polyfunctional reagents, both homo- and hetero-functional (such as those described in the catalog of the Pierce Chemical Co., Rockford, IL), may be employed as the linker group. Coupling may be effected, for example, through amino groups, carboxyl groups, 5 sulfhydryl groups or oxidized carbohydrate residues. There are numerous references describing such methodology, *e.g.*, U.S. Patent No. 4,671,958, to Rodwell et al.

Where a therapeutic agent is more potent when free from the antibody portion of the immunoconjugates of the present invention, it may be desirable to use a linker group which is cleavable during or upon internalization into a cell. A number of different cleavable linker groups have been described. The mechanisms for the intracellular release of an agent from these linker groups include cleavage by reduction of a disulfide bond (*e.g.*, U.S. Patent No. 4,489,710, to Spitler), by irradiation of a photolabile bond (*e.g.*, U.S. Patent No. 4,625,014, to Senter et al.), by hydrolysis of 15 derivatized amino acid side chains (*e.g.*, U.S. Patent No. 4,638,045, to Kohn et al.), by serum complement-mediated hydrolysis (*e.g.*, U.S. Patent No. 4,671,958, to Rodwell et al.), and acid-catalyzed hydrolysis (*e.g.*, U.S. Patent No. 4,569,789, to Blattler et al.).

It may be desirable to couple more than one agent to an antibody. In one embodiment, multiple molecules of an agent are coupled to one antibody molecule. In another embodiment, more than one type of agent may be coupled to one antibody. Regardless of the particular embodiment, immunoconjugates with more than one agent may be prepared in a variety of ways. For example, more than one agent may be coupled directly to an antibody molecule, or linkers that provide multiple sites for 25 attachment can be used. Alternatively, a carrier can be used.

A carrier may bear the agents in a variety of ways, including covalent bonding either directly or via a linker group. Suitable carriers include proteins such as albumins (*e.g.*, U.S. Patent No. 4,507,234, to Kato et al.), peptides and polysaccharides such as aminodextran (*e.g.*, U.S. Patent No. 4,699,784, to Shih et al.). A carrier may 30 also bear an agent by noncovalent bonding or by encapsulation, such as within a liposome vesicle (*e.g.*, U.S. Patent Nos. 4,429,008 and 4,873,088). Carriers specific for

radionuclide agents include radiohalogenated small molecules and chelating compounds. For example, U.S. Patent No. 4,735,792 discloses representative radiohalogenated small molecules and their synthesis. A radionuclide chelate may be formed from chelating compounds that include those containing nitrogen and sulfur atoms as the donor atoms for binding the metal, or metal oxide, radionuclide. For example, U.S. Patent No. 4,673,562, to Davison et al. discloses representative chelating compounds and their synthesis.

A variety of routes of administration for the antibodies and immunoconjugates may be used. Typically, administration will be intravenous, intramuscular, subcutaneous or in the bed of a resected tumor. It will be evident that the precise dose of the antibody/immunoconjugate will vary depending upon the antibody used, the antigen density on the tumor, and the rate of clearance of the antibody.

#### T CELLS

Immunotherapeutic compositions may also, or alternatively, comprise T cells specific for an ovarian tumor protein. Such cells may generally be prepared *in vitro* or *ex vivo*, using standard procedures. For example, T cells may be isolated from bone marrow, peripheral blood or a fraction of bone marrow or peripheral blood of a patient, using a commercially available cell separation system, such as the CEPRATE™ system, available from CellPro Inc., Bothell WA (see also U.S. Patent No. 5,240,856; U.S. Patent No. 5,215,926; WO 89/06280; WO 91/16116 and WO 92/07243). Alternatively, T cells may be derived from related or unrelated humans, non-human mammals, cell lines or cultures.

T cells may be stimulated with an ovarian tumor polypeptide, polynucleotide encoding an ovarian tumor polypeptide and/or an antigen presenting cell (APC) that expresses such a polypeptide. Such stimulation is performed under conditions and for a time sufficient to permit the generation of T cells that are specific for the polypeptide. Preferably, an ovarian tumor polypeptide or polynucleotide is present within a delivery vehicle, such as a microsphere, to facilitate the generation of specific T cells.

T cells are considered to be specific for an ovarian tumor polypeptide if the T cells kill target cells coated with the polypeptide or expressing a gene encoding the polypeptide. T cell specificity may be evaluated using any of a variety of standard techniques. For example, within a chromium release assay or proliferation assay, a stimulation index of more than two fold increase in lysis and/or proliferation, compared to negative controls, indicates T cell specificity. Such assays may be performed, for example, as described in Chen et al., *Cancer Res.* 54:1065-1070, 1994. Alternatively, detection of the proliferation of T cells may be accomplished by a variety of known techniques. For example, T cell proliferation can be detected by measuring an increased rate of DNA synthesis (*e.g.*, by pulse-labeling cultures of T cells with tritiated thymidine and measuring the amount of tritiated thymidine incorporated into DNA). Contact with an ovarian tumor polypeptide (100 ng/ml - 100 µg/ml, preferably 200 ng/ml - 25 µg/ml) for 3 - 7 days should result in at least a two fold increase in proliferation of the T cells. Contact as described above for 2-3 hours should result in activation of the T cells, as measured using standard cytokine assays in which a two fold increase in the level of cytokine release (*e.g.*, TNF or IFN-γ) is indicative of T cell activation (*see* Coligan et al., *Current Protocols in Immunology*, vol. 1, Wiley Interscience (Greene 1998)). T cells that have been activated in response to an ovarian tumor polypeptide, polynucleotide or polypeptide-expressing APC may be CD4<sup>+</sup> and/or CD8<sup>+</sup>. Ovarian tumor protein-specific T cells may be expanded using standard techniques. Within preferred embodiments, the T cells are derived from a patient, or from a related or unrelated donor, and are administered to the patient following stimulation and expansion.

For therapeutic purposes, CD4<sup>+</sup> or CD8<sup>+</sup> T cells that proliferate in response to an ovarian tumor polypeptide, polynucleotide or APC can be expanded in number either *in vitro* or *in vivo*. Proliferation of such T cells *in vitro* may be accomplished in a variety of ways. For example, the T cells can be re-exposed to an ovarian tumor polypeptide (*e.g.*, a short peptide corresponding to an immunogenic portion of such a polypeptide) with or without the addition of T cell growth factors, such as interleukin-2, and/or stimulator cells that synthesize an ovarian tumor polypeptide. Alternatively, one or more T cells that proliferate in the presence of an

ovarian tumor protein can be expanded in number by cloning. Methods for cloning cells are well known in the art, and include limiting dilution. Following expansion, the cells may be administered back to the patient as described, for example, by Chang et al., *Crit. Rev. Oncol. Hematol.* 22:213, 1996.

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#### PHARMACEUTICAL COMPOSITIONS AND VACCINES

Within certain aspects, polypeptides, polynucleotides, T cells and/or binding agents described herein may be incorporated into pharmaceutical compositions or immunogenic compositions (*i.e.*, vaccines). Pharmaceutical compositions comprise one or more such compounds and a physiologically acceptable carrier. Vaccines may comprise one or more such compounds and a non-specific immune response enhancer. A non-specific immune response enhancer may be any substance that enhances an immune response to an exogenous antigen. Examples of non-specific immune response enhancers include adjuvants, biodegradable microspheres (*e.g.*, polylactic galactide) and liposomes (into which the compound is incorporated; *see e.g.*, Fullerton, U.S. Patent No. 4,235,877). Vaccine preparation is generally described in, for example, M.F. Powell and M.J. Newman, eds., "Vaccine Design (the subunit and adjuvant approach)," Plenum Press (NY, 1995). Vaccines may be designed to generate antibody immunity and/or cellular immunity such as that arising from CTL or CD4+ T cells.

Pharmaceutical compositions and vaccines within the scope of the present invention may also contain other compounds, which may be biologically active or inactive. For example, one or more immunogenic portions of other tumor antigens may be present, either incorporated into a fusion polypeptide or as a separate compound, within the composition or vaccine. Polypeptides may, but need not, be conjugated to other macromolecules as described, for example, within US Patent Nos. 4,372,945 and 4,474,757. Pharmaceutical compositions and vaccines may generally be used for prophylactic and therapeutic purposes.

A pharmaceutical composition or vaccine may contain a polynucleotide encoding one or more of the polypeptides as described above, such that the polypeptide is generated *in situ*. Such a polynucleotide may comprise DNA, RNA, a modified nucleic acid or a DNA/RNA hybrid. As noted above, a polynucleotide may be present

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within any of a variety of delivery systems known to those of ordinary skill in the art, including nucleic acid expression systems, bacteria and viral expression systems. Numerous gene delivery techniques are well known in the art, such as those described by Rolland, *Crit. Rev. Therap. Drug Carrier Systems* 15:143-198, 1998, and references  
5 cited therein. Appropriate nucleic acid expression systems contain the necessary DNA sequences for expression in the patient (such as a suitable promoter and terminating signal). Bacterial delivery systems involve the administration of a bacterium (such as *Bacillus-Calmette-Guerrin*) that expresses an immunogenic portion of the polypeptide on its cell surface or secretes such an epitope. In a preferred embodiment, the DNA  
10 may be introduced using a viral expression system (e.g., vaccinia or other pox virus, retrovirus, or adenovirus), which may involve the use of a non-pathogenic (defective), replication competent virus. Suitable systems are disclosed, for example, in Fisher-Hoch et al., *Proc. Natl. Acad. Sci. USA* 86:317-321, 1989; Flexner et al., *Ann. N.Y. Acad. Sci.* 569:86-103, 1989; Flexner et al., *Vaccine* 8:17-21, 1990; U.S. Patent  
15 Nos. 4,603,112, 4,769,330, and 5,017,487; WO 89/01973; U.S. Patent No. 4,777,127; GB 2,200,651; EP 0,345,242; WO 91/02805; Berkner, *Biotechniques* 6:616-627, 1988; Rosenfeld et al., *Science* 252:431-434, 1991; Kolls et al., *Proc. Natl. Acad. Sci. USA* 91:215-219, 1994; Kass-Eisler et al., *Proc. Natl. Acad. Sci. USA* 90:11498-11502, 1993; Guzman et al., *Circulation* 88:2838-2848, 1993; and Guzman et al., *Cir. Res.*  
20 73:1202-1207, 1993. Techniques for incorporating DNA into such expression systems are well known to those of ordinary skill in the art. The DNA may also be "naked," as described, for example, in Ulmer et al., *Science* 259:1745-1749, 1993 and reviewed by Cohen, *Science* 259:1691-1692, 1993. The uptake of naked DNA may be increased by coating the DNA onto biodegradable beads, which are efficiently transported into the  
25 cells. It will be apparent that a vaccine may comprise both a polynucleotide and a polypeptide component. Such vaccines may provide for an enhanced immune response.

It will be apparent that a vaccine may contain pharmaceutically acceptable salts of the polynucleotides and polypeptides provided herein. Such salts may be prepared from pharmaceutically acceptable non-toxic bases, including organic  
30 bases (e.g., salts of primary, secondary and tertiary amines and basic amino acids) and



inorganic bases (*e.g.*, sodium, potassium, lithium, ammonium, calcium and magnesium salts).

While any suitable carrier known to those of ordinary skill in the art may be employed in the pharmaceutical compositions of this invention, the type of carrier will vary depending on the mode of administration. Compositions of the present invention may be formulated for any appropriate manner of administration, including for example, topical, oral, nasal, intravenous, intracranial, intraperitoneal, subcutaneous or intramuscular administration. For parenteral administration, such as subcutaneous injection, the carrier preferably comprises water, saline, alcohol, a fat, a wax or a buffer. For oral administration, any of the above carriers or a solid carrier, such as mannitol, lactose, starch, magnesium stearate, sodium saccharine, talcum, cellulose, glucose, sucrose, and magnesium carbonate, may be employed. Biodegradable microspheres (*e.g.*, polylactate polyglycolate) may also be employed as carriers for the pharmaceutical compositions of this invention. Suitable biodegradable microspheres are disclosed, for example, in U.S. Patent Nos. 4,897,268; 5,075,109; 5,928,647; 5,811,128; 5,820,883; 5,853,763; 5,814,344 and 5,942,252.

Such compositions may also comprise buffers (*e.g.*, neutral buffered saline or phosphate buffered saline), carbohydrates (*e.g.*, glucose, mannose, sucrose or dextrans), mannitol, proteins, polypeptides or amino acids such as glycine, antioxidants, bacteriostats, chelating agents such as EDTA or glutathione, adjuvants (*e.g.*, aluminum hydroxide), solutes that render the formulation isotonic, hypotonic or weakly hypertonic with the blood of a recipient, suspending agents, thickening agents and/or preservatives. Alternatively, compositions of the present invention may be formulated as a lyophilizate. Compounds may also be encapsulated within liposomes using well known technology.

Any of a variety of non-specific immune response enhancers may be employed in the vaccines of this invention. For example, an adjuvant may be included. Most adjuvants contain a substance designed to protect the antigen from rapid catabolism, such as aluminum hydroxide or mineral oil, and a stimulator of immune responses, such as lipid A, *Bordetella pertussis* or *Mycobacterium tuberculosis* derived proteins. Suitable adjuvants are commercially available as, for example, Freund's

Incomplete Adjuvant and Complete Adjuvant (Difco Laboratories, Detroit, MI); Merck Adjuvant 65 (Merck and Company, Inc., Rahway, NJ); AS-2 (SmithKline Beecham); aluminum salts such as aluminum hydroxide gel (alum) or aluminum phosphate; salts of calcium, iron or zinc; an insoluble suspension of acylated tyrosine; acylated sugars;  
5 cationically or anionically derivatized polysaccharides; polyphosphazenes; biodegradable microspheres; monophosphoryl lipid A and quil A. Cytokines, such as GM-CSF or interleukin-2, -7, or -12, may also be used as adjuvants.

Within the vaccines provided herein, the adjuvant composition is preferably designed to induce an immune response predominantly of the Th1 type.  
10 High levels of Th1-type cytokines (*e.g.*, IFN- $\gamma$ , TNF- $\alpha$ , IL-2 and IL-12) tend to favor the induction of cell mediated immune responses to an administered antigen. In contrast, high levels of Th2-type cytokines (*e.g.*, IL-4, IL-5, IL-6 and IL-10) tend to favor the induction of humoral immune responses. Following application of a vaccine as provided herein, a patient will support an immune response that includes Th1- and Th2-  
15 type responses. Within a preferred embodiment, in which a response is predominantly Th1-type, the level of Th1-type cytokines will increase to a greater extent than the level of Th2-type cytokines. The levels of these cytokines may be readily assessed using standard assays. For a review of the families of cytokines, see Mosmann and Coffman, *Ann. Rev. Immunol.* 7:145-173, 1989.

20 Preferred adjuvants for use in eliciting a predominantly Th1-type response include, for example, a combination of monophosphoryl lipid A, preferably 3-de-O-acylated monophosphoryl lipid A (3D-MPL), together with an aluminum salt. MPL adjuvants are available from Ribi ImmunoChem Research Inc. (Hamilton, MT; *see* US Patent Nos. 4,436,727; 4,877,611; 4,866,034 and 4,912,094). CpG-containing  
25 oligonucleotides (in which the CpG dinucleotide is unmethylated) also induce a predominantly Th1 response. Such oligonucleotides are well known and are described, for example, in WO 96/02555 and WP 99/33488. Immunostimulatory DNA sequences are also described, for example, by Sato et al., *Science* 273:352, 1996. Another preferred adjuvant is a saponin, preferably QS21 (Aquila, United States), which may be  
30 used alone or in combination with other adjuvants. For example, an enhanced system involves the combination of a monophosphoryl lipid A and saponin derivative, such as

the combination of QS21 and 3D-MPL as described in WO 94/00153, or a less reactogenic composition where the QS21 is quenched with cholesterol, as described in WO 96/33739. Other preferred formulations comprise an oil-in-water emulsion and tocopherol. A particularly potent adjuvant formulation involving QS21, 3D-MPL and  
5 tocopherol in an oil-in-water emulsion is described in WO 95/17210.

Other preferred adjuvants include Montanide ISA 720 (Seppic, France), SAF (Chiron, California, United States), ISCOMS (CSL), MF-59 (Chiron), the SBAS series of adjuvants (*e.g.*, SBAS-2 or SBAS-4, available from SmithKline Beecham, Rixensart, Belgium), Detox (Ribi ImmunoChem Research Inc., Hamilton, MT), RC-529  
10 (Ribi ImmunoChem Research Inc., Hamilton, MT) and Aminoalkyl glucosaminide 4-phosphates (AGPs).

Any vaccine provided herein may be prepared using well known methods that result in a combination of antigen, immune response enhancer and a suitable carrier or excipient. The compositions described herein may be administered as  
15 part of a sustained release formulation (*i.e.*, a formulation such as a capsule or sponge that effects a slow release of compound following administration). Such formulations may generally be prepared using well known technology (*see, e.g.*, Coombes et al., *Vaccine* 14:1429-1438, 1996) and administered by, for example, oral, rectal or subcutaneous implantation, or by implantation at the desired target site. Sustained-  
20 release formulations may contain a polypeptide, polynucleotide or antibody dispersed in a carrier matrix and/or contained within a reservoir surrounded by a rate controlling membrane.

Carriers for use within such formulations are biocompatible, and may also be biodegradable; preferably the formulation provides a relatively constant level of  
25 active component release. Such carriers include microparticles of poly(lactide-co-glycolide), as well as polyacrylate, latex, starch, cellulose and dextran. Other delayed-release carriers include supramolecular biovectors, which comprise a non-liquid hydrophilic core (*e.g.*, a cross-linked polysaccharide or oligosaccharide) and, optionally, an external layer comprising an amphiphilic compound, such as a phospholipid (*see*  
30 *e.g.*, U.S. Patent No. 5, 151, 254 and PCT applications WO 94/20078, WO/94/23701 and WO 96/06638). The amount of active compound contained within a sustained

release formulation depends upon the site of implantation, the rate and expected duration of release and the nature of the condition to be treated or prevented.

Any of a variety of delivery vehicles may be employed within pharmaceutical compositions and vaccines to facilitate production of an antigen-specific  
5 immune response that targets tumor cells. Delivery vehicles include antigen presenting cells (APCs), such as dendritic cells, macrophages, B cells, monocytes and other cells that may be engineered to be efficient APCs. Such cells may, but need not, be genetically modified to increase the capacity for presenting the antigen, to improve activation and/or maintenance of the T cell response, to have anti-tumor effects *per se*  
10 and/or to be immunologically compatible with the receiver (*i.e.*, matched HLA haplotype). APCs may generally be isolated from any of a variety of biological fluids and organs, including tumor and peritumoral tissues, and may be autologous, allogeneic, syngeneic or xenogeneic cells.

Certain preferred embodiments of the present invention use dendritic  
15 cells or progenitors thereof as antigen-presenting cells. Dendritic cells are highly potent APCs (Banchereau and Steinman, *Nature* 392:245-251, 1998) and have been shown to be effective as a physiological adjuvant for eliciting prophylactic or therapeutic antitumor immunity (*see* Timmerman and Levy, *Ann. Rev. Med.* 50:507-529, 1999). In general, dendritic cells may be identified based on their typical shape (stellate *in situ*,  
20 with marked cytoplasmic processes (dendrites) visible *in vitro*), their ability to take up process and present antigens with high efficiency and their ability to activate naïve T cell responses. Dendritic cells may, of course, be engineered to express specific cell-surface receptors or ligands that are not commonly found on dendritic cells *in vivo* or *ex vivo*, and such modified dendritic cells are contemplated by the present invention. As  
25 an alternative to dendritic cells, secreted vesicles antigen-loaded dendritic cells (called exosomes) may be used within a vaccine (*see* Zitvogel et al., *Nature Med.* 4:594-600, 1998).

Dendritic cells and progenitors may be obtained from peripheral blood, bone marrow, tumor-infiltrating cells, peritumoral tissues-infiltrating cells, lymph  
30 nodes, spleen, skin, umbilical cord blood or any other suitable tissue or fluid. For example, dendritic cells may be differentiated *ex vivo* by adding a combination of

cytokines such as GM-CSF, IL-4, IL-13 and/or TNF $\alpha$  to cultures of monocytes harvested from peripheral blood. Alternatively, CD34 positive cells harvested from peripheral blood, umbilical cord blood or bone marrow may be differentiated into dendritic cells by adding to the culture medium combinations of GM-CSF, IL-3, TNF $\alpha$ ,  
5 CD40 ligand, LPS, flt3 ligand and/or other compound(s) that induce maturation and proliferation of dendritic cells.

Dendritic cells are conveniently categorized as "immature" and "mature" cells, which allows a simple way to discriminate between two well characterized phenotypes. However, this nomenclature should not be construed to exclude all  
10 possible intermediate stages of differentiation. Immature dendritic cells are characterized as APC with a high capacity for antigen uptake and processing, which correlates with the high expression of Fc $\gamma$  receptor and mannose receptor. The mature phenotype is typically characterized by a lower expression of these markers, but a high expression of cell surface molecules responsible for T cell activation such as class I and  
15 class II MHC, adhesion molecules (*e.g.*, CD54 and CD11) and costimulatory molecules (*e.g.*, CD40, CD80, CD86 and 4-1BB).

APCs may generally be transfected with a polynucleotide encoding an ovarian tumor protein (or portion or other variant thereof) such that the ovarian tumor polypeptide, or an immunogenic portion thereof, is expressed on the cell surface. Such  
20 transfection may take place *ex vivo*, and a composition or vaccine comprising such transfected cells may then be used for therapeutic purposes, as described herein. Alternatively, a gene delivery vehicle that targets a dendritic or other antigen presenting cell may be administered to a patient, resulting in transfection that occurs *in vivo*. *In vivo* and *ex vivo* transfection of dendritic cells, for example, may generally be performed  
25 using any methods known in the art, such as those described in WO 97/24447, or the gene gun approach described by Mahvi et al., *Immunology and cell Biology* 75:456-460, 1997. Antigen loading of dendritic cells may be achieved by incubating dendritic cells or progenitor cells with the ovarian tumor polypeptide, DNA (naked or within a plasmid vector) or RNA; or with antigen-expressing recombinant bacterium or viruses (*e.g.*,  
30 vaccinia, fowlpox, adenovirus or lentivirus vectors). Prior to loading, the polypeptide may be covalently conjugated to an immunological partner that provides T cell help

(e.g., a carrier molecule). Alternatively, a dendritic cell may be pulsed with a non-conjugated immunological partner, separately or in the presence of the polypeptide.

Vaccines and pharmaceutical compositions may be presented in unit-dose or multi-dose containers, such as sealed ampoules or vials. Such containers are preferably hermetically sealed to preserve sterility of the formulation until use. In general, formulations may be stored as suspensions, solutions or emulsions in oily or aqueous vehicles. Alternatively, a vaccine or pharmaceutical composition may be stored in a freeze-dried condition requiring only the addition of a sterile liquid carrier immediately prior to use.

10

#### CANCER THERAPY

In further aspects of the present invention, the compositions described herein may be used for immunotherapy of cancer, such as ovarian cancer. Within such methods, pharmaceutical compositions and vaccines are typically administered to a patient. As used herein, a "patient" refers to any warm-blooded animal, preferably a human. A patient may or may not be afflicted with cancer. Accordingly, the above pharmaceutical compositions and vaccines may be used to prevent the development of a cancer or to treat a patient afflicted with a cancer. A cancer may be diagnosed using criteria generally accepted in the art, including the presence of a malignant tumor. Pharmaceutical compositions and vaccines may be administered either prior to or following surgical removal of primary tumors and/or treatment such as administration of radiotherapy or conventional chemotherapeutic drugs. Administration may be by any suitable method, including administration by intravenous, intraperitoneal, intramuscular, subcutaneous, intranasal, intradermal, anal, vaginal, topical and oral routes.

Within certain embodiments, immunotherapy may be active immunotherapy, in which treatment relies on the *in vivo* stimulation of the endogenous host immune system to react against tumors with the administration of immune response-modifying agents (such as polypeptides and polynucleotides as provided herein).

30

Within other embodiments, immunotherapy may be passive immunotherapy, in which treatment involves the delivery of agents with established tumor-immune reactivity (such as effector cells or antibodies) that can directly or indirectly mediate antitumor effects and does not necessarily depend on an intact host immune system. Examples of effector cells include T cells as discussed above, T lymphocytes (such as CD8<sup>+</sup> cytotoxic T lymphocytes and CD4<sup>+</sup> T-helper tumor-infiltrating lymphocytes), killer cells (such as Natural Killer cells and lymphokine-activated killer cells), B cells and antigen-presenting cells (such as dendritic cells and macrophages) expressing a polypeptide provided herein. T cell receptors and antibody receptors specific for the polypeptides recited herein may be cloned, expressed and transferred into other vectors or effector cells for adoptive immunotherapy. The polypeptides provided herein may also be used to generate antibodies or anti-idiotypic antibodies (as described above and in U.S. Patent No. 4,918,164) for passive immunotherapy.

Effector cells may generally be obtained in sufficient quantities for adoptive immunotherapy by growth *in vitro*, as described herein. Culture conditions for expanding single antigen-specific effector cells to several billion in number with retention of antigen recognition *in vivo* are well known in the art. Such *in vitro* culture conditions typically use intermittent stimulation with antigen, often in the presence of cytokines (such as IL-2) and non-dividing feeder cells. As noted above, immunoreactive polypeptides as provided herein may be used to rapidly expand antigen-specific T cell cultures in order to generate a sufficient number of cells for immunotherapy. In particular, antigen-presenting cells, such as dendritic, macrophage or B cells, may be pulsed with immunoreactive polypeptides or transfected with one or more polynucleotides using standard techniques well known in the art. For example, antigen-presenting cells can be transfected with a polynucleotide having a promoter appropriate for increasing expression in a recombinant virus or other expression system. Cultured effector cells for use in therapy must be able to grow and distribute widely, and to survive long term *in vivo*. Studies have shown that cultured effector cells can be induced to grow *in vivo* and to survive long term in substantial numbers by repeated

stimulation with antigen supplemented with IL-2 (*see*, for example, Cheever et al., *Immunological Reviews* 157:177, 1997).

Alternatively, a vector expressing a polypeptide recited herein may be introduced into antigen presenting cells taken from a patient and clonally propagated *ex vivo* for transplant back into the same patient. Transfected cells may be reintroduced into the patient using any means known in the art, preferably in sterile form by intravenous, intracavitary, intraperitoneal or intratumor administration.

Routes and frequency of administration of the therapeutic compositions described herein, as well as dosage, will vary from individual to individual, and may be readily established using standard techniques. In general, the pharmaceutical compositions and vaccines may be administered by injection (*e.g.*, intracutaneous, intramuscular, intravenous or subcutaneous), intranasally (*e.g.*, by aspiration) or orally. Preferably, between 1 and 10 doses may be administered over a 52 week period. Preferably, 6 doses are administered, at intervals of 1 month, and booster vaccinations may be given periodically thereafter. Alternate protocols may be appropriate for individual patients. A suitable dose is an amount of a compound that, when administered as described above, is capable of promoting an anti-tumor immune response, and is at least 10-50% above the basal (*i.e.*, untreated) level. Such response can be monitored by measuring the anti-tumor antibodies in a patient or by vaccine-dependent generation of cytolytic effector cells capable of killing the patient's tumor cells *in vitro*. Such vaccines should also be capable of causing an immune response that leads to an improved clinical outcome (*e.g.*, more frequent remissions, complete or partial or longer disease-free survival) in vaccinated patients as compared to non-vaccinated patients. In general, for pharmaceutical compositions and vaccines comprising one or more polypeptides, the amount of each polypeptide present in a dose ranges from about 1  $\mu$ g to 5 mg, preferably 100  $\mu$ g to 5 mg per kg of host. Suitable dose sizes will vary with the size of the patient, but will typically range from about 0.1 mL to about 5 mL.

In general, an appropriate dosage and treatment regimen provides the active compound(s) in an amount sufficient to provide therapeutic and/or prophylactic benefit. Such a response can be monitored by establishing an improved clinical



outcome (e.g., more frequent remissions, complete or partial, or longer disease-free survival) in treated patients as compared to non-treated patients. Increases in preexisting immune responses to an ovarian tumor protein generally correlate with an improved clinical outcome. Such immune responses may generally be evaluated using  
5 standard proliferation, cytotoxicity or cytokine assays, which may be performed using samples obtained from a patient before and after treatment.

#### METHODS FOR DETECTING CANCER

In general, a cancer may be detected in a patient based on the presence of  
10 one or more ovarian tumor proteins and/or polynucleotides encoding such proteins in a biological sample (such as blood, sera, urine and/or tumor biopsies) obtained from the patient. In other words, such proteins may be used as markers to indicate the presence or absence of a cancer such as ovarian cancer. In addition, such proteins may be useful for the detection of other cancers. The binding agents provided herein generally permit  
15 detection of the level of antigen that binds to the agent in the biological sample. Polynucleotide primers and probes may be used to detect the level of mRNA encoding a tumor protein, which is also indicative of the presence or absence of a cancer. In general, an ovarian tumor sequence should be present at a level that is at least three fold higher in tumor tissue than in normal tissue.

20 There are a variety of assay formats known to those of ordinary skill in the art for using a binding agent to detect polypeptide markers in a sample. *See, e.g.,* Harlow and Lane, *Antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratory, 1988. In general, the presence or absence of a cancer in a patient may be determined by (a) contacting a biological sample obtained from a patient with a binding agent; (b)  
25 detecting in the sample a level of polypeptide that binds to the binding agent; and (c) comparing the level of polypeptide with a predetermined cut-off value.

In a preferred embodiment, the assay involves the use of binding agent immobilized on a solid support to bind to and remove the polypeptide from the remainder of the sample. The bound polypeptide may then be detected using a detection  
30 reagent that contains a reporter group and specifically binds to the binding agent/polypeptide complex. Such detection reagents may comprise, for example, a

binding agent that specifically binds to the polypeptide or an antibody or other agent that specifically binds to the binding agent, such as an anti-immunoglobulin, protein G, protein A or a lectin. Alternatively, a competitive assay may be utilized, in which a polypeptide is labeled with a reporter group and allowed to bind to the immobilized binding agent after incubation of the binding agent with the sample. The extent to which components of the sample inhibit the binding of the labeled polypeptide to the binding agent is indicative of the reactivity of the sample with the immobilized binding agent. Suitable polypeptides for use within such assays include full length ovarian tumor proteins and portions thereof to which the binding agent binds, as described above.

The solid support may be any material known to those of ordinary skill in the art to which the tumor protein may be attached. For example, the solid support may be a test well in a microtiter plate or a nitrocellulose or other suitable membrane. Alternatively, the support may be a bead or disc, such as glass, fiberglass, latex or a plastic material such as polystyrene or polyvinylchloride. The support may also be a magnetic particle or a fiber optic sensor, such as those disclosed, for example, in U.S. Patent No. 5,359,681. The binding agent may be immobilized on the solid support using a variety of techniques known to those of skill in the art, which are amply described in the patent and scientific literature. In the context of the present invention, the term "immobilization" refers to both noncovalent association, such as adsorption, and covalent attachment (which may be a direct linkage between the agent and functional groups on the support or may be a linkage by way of a cross-linking agent). Immobilization by adsorption to a well in a microtiter plate or to a membrane is preferred. In such cases, adsorption may be achieved by contacting the binding agent, in a suitable buffer, with the solid support for a suitable amount of time. The contact time varies with temperature, but is typically between about 1 hour and about 1 day. In general, contacting a well of a plastic microtiter plate (such as polystyrene or polyvinylchloride) with an amount of binding agent ranging from about 10 ng to about 10  $\mu$ g, and preferably about 100 ng to about 1  $\mu$ g, is sufficient to immobilize an adequate amount of binding agent.

Covalent attachment of binding agent to a solid support may generally be achieved by first reacting the support with a bifunctional reagent that will react with both the support and a functional group, such as a hydroxyl or amino group, on the binding agent. For example, the binding agent may be covalently attached to supports  
5 having an appropriate polymer coating using benzoquinone or by condensation of an aldehyde group on the support with an amine and an active hydrogen on the binding partner (*see, e.g.*, Pierce Immunotechnology Catalog and Handbook, 1991, at A12-A13).

In certain embodiments, the assay is a two-antibody sandwich assay.  
10 This assay may be performed by first contacting an antibody that has been immobilized on a solid support, commonly the well of a microtiter plate, with the sample, such that polypeptides within the sample are allowed to bind to the immobilized antibody. Unbound sample is then removed from the immobilized polypeptide-antibody complexes and a detection reagent (preferably a second antibody capable of binding to a  
15 different site on the polypeptide) containing a reporter group is added. The amount of detection reagent that remains bound to the solid support is then determined using a method appropriate for the specific reporter group.

More specifically, once the antibody is immobilized on the support as described above, the remaining protein binding sites on the support are typically  
20 blocked. Any suitable blocking agent known to those of ordinary skill in the art, such as bovine serum albumin or Tween 20™ (Sigma Chemical Co., St. Louis, MO). The immobilized antibody is then incubated with the sample, and polypeptide is allowed to bind to the antibody. The sample may be diluted with a suitable diluent, such as phosphate-buffered saline (PBS) prior to incubation. In general, an appropriate contact  
25 time (*i.e.*, incubation time) is a period of time that is sufficient to detect the presence of polypeptide within a sample obtained from an individual with ovarian cancer. Preferably, the contact time is sufficient to achieve a level of binding that is at least about 95% of that achieved at equilibrium between bound and unbound polypeptide. Those of ordinary skill in the art will recognize that the time necessary to achieve  
30 equilibrium may be readily determined by assaying the level of binding that occurs over

a period of time. At room temperature, an incubation time of about 30 minutes is generally sufficient.

Unbound sample may then be removed by washing the solid support with an appropriate buffer, such as PBS containing 0.1% Tween 20™. The second  
5 antibody, which contains a reporter group, may then be added to the solid support. Preferred reporter groups include those groups recited above.

The detection reagent is then incubated with the immobilized antibody-polypeptide complex for an amount of time sufficient to detect the bound polypeptide. An appropriate amount of time may generally be determined by assaying the level of  
10 binding that occurs over a period of time. Unbound detection reagent is then removed and bound detection reagent is detected using the reporter group. The method employed for detecting the reporter group depends upon the nature of the reporter group. For radioactive groups, scintillation counting or autoradiographic methods are generally appropriate. Spectroscopic methods may be used to detect dyes, luminescent groups  
15 and fluorescent groups. Biotin may be detected using avidin, coupled to a different reporter group (commonly a radioactive or fluorescent group or an enzyme). Enzyme reporter groups may generally be detected by the addition of substrate (generally for a specific period of time), followed by spectroscopic or other analysis of the reaction products.

20 To determine the presence or absence of a cancer, such as ovarian cancer, the signal detected from the reporter group that remains bound to the solid support is generally compared to a signal that corresponds to a predetermined cut-off value. In one preferred embodiment, the cut-off value for the detection of a cancer is the average mean signal obtained when the immobilized antibody is incubated with  
25 samples from patients without the cancer. In general, a sample generating a signal that is three standard deviations above the predetermined cut-off value is considered positive for the cancer. In an alternate preferred embodiment, the cut-off value is determined using a Receiver Operator Curve, according to the method of Sackett et al., *Clinical Epidemiology: A Basic Science for Clinical Medicine*, Little Brown and Co., 1985,  
30 p. 106-7. Briefly, in this embodiment, the cut-off value may be determined from a plot of pairs of true positive rates (*i.e.*, sensitivity) and false positive rates (100%-specificity)

that correspond to each possible cut-off value for the diagnostic test result. The cut-off value on the plot that is the closest to the upper left-hand corner (*i.e.*, the value that encloses the largest area) is the most accurate cut-off value, and a sample generating a signal that is higher than the cut-off value determined by this method may be considered  
5 positive. Alternatively, the cut-off value may be shifted to the left along the plot, to minimize the false positive rate, or to the right, to minimize the false negative rate. In general, a sample generating a signal that is higher than the cut-off value determined by this method is considered positive for a cancer.

In a related embodiment, the assay is performed in a flow-through or  
10 strip test format, wherein the binding agent is immobilized on a membrane, such as nitrocellulose. In the flow-through test, polypeptides within the sample bind to the immobilized binding agent as the sample passes through the membrane. A second, labeled binding agent then binds to the binding agent-polypeptide complex as a solution containing the second binding agent flows through the membrane. The detection of  
15 bound second binding agent may then be performed as described above. In the strip test format, one end of the membrane to which binding agent is bound is immersed in a solution containing the sample. The sample migrates along the membrane through a region containing second binding agent and to the area of immobilized binding agent. Concentration of second binding agent at the area of immobilized antibody indicates the  
20 presence of a cancer. Typically, the concentration of second binding agent at that site generates a pattern, such as a line, that can be read visually. The absence of such a pattern indicates a negative result. In general, the amount of binding agent immobilized on the membrane is selected to generate a visually discernible pattern when the biological sample contains a level of polypeptide that would be sufficient to generate a  
25 positive signal in the two-antibody sandwich assay, in the format discussed above. Preferred binding agents for use in such assays are antibodies and antigen-binding fragments thereof. Preferably, the amount of antibody immobilized on the membrane ranges from about 25 ng to about 1µg, and more preferably from about 50 ng to about 500 ng. Such tests can typically be performed with a very small amount of biological  
30 sample.

Of course, numerous other assay protocols exist that are suitable for use with the tumor proteins or binding agents of the present invention. The above descriptions are intended to be exemplary only. For example, it will be apparent to those of ordinary skill in the art that the above protocols may be readily modified to use ovarian tumor polypeptides to detect antibodies that bind to such polypeptides in a biological sample. The detection of such ovarian tumor protein specific antibodies may correlate with the presence of a cancer.

A cancer may also, or alternatively, be detected based on the presence of T cells that specifically react with an ovarian tumor protein in a biological sample. Within certain methods, a biological sample comprising CD4<sup>+</sup> and/or CD8<sup>+</sup> T cells isolated from a patient is incubated with an ovarian tumor polypeptide, a polynucleotide encoding such a polypeptide and/or an APC that expresses at least an immunogenic portion of such a polypeptide, and the presence or absence of specific activation of the T cells is detected. Suitable biological samples include, but are not limited to, isolated T cells. For example, T cells may be isolated from a patient by routine techniques (such as by Ficoll/Hypaque density gradient centrifugation of peripheral blood lymphocytes). T cells may be incubated *in vitro* for 2-9 days (typically 4 days) at 37°C with Mtb-81 or Mtb-67.2 polypeptide (*e.g.*, 5 - 25 µg/ml). It may be desirable to incubate another aliquot of a T cell sample in the absence of ovarian tumor polypeptide to serve as a control. For CD4<sup>+</sup> T cells, activation is preferably detected by evaluating proliferation of the T cells. For CD8<sup>+</sup> T cells, activation is preferably detected by evaluating cytolytic activity. A level of proliferation that is at least two fold greater and/or a level of cytolytic activity that is at least 20% greater than in disease-free patients indicates the presence of a cancer in the patient.

As noted above, a cancer may also, or alternatively, be detected based on the level of mRNA encoding an ovarian tumor protein in a biological sample. For example, at least two oligonucleotide primers may be employed in a polymerase chain reaction (PCR) based assay to amplify a portion of an ovarian tumor cDNA derived from a biological sample, wherein at least one of the oligonucleotide primers is specific for (*i.e.*, hybridizes to) a polynucleotide encoding the ovarian tumor protein. The amplified cDNA is then separated and detected using techniques well known in the art,

such as gel electrophoresis. Similarly, oligonucleotide probes that specifically hybridize to a polynucleotide encoding an ovarian tumor protein may be used in a hybridization assay to detect the presence of polynucleotide encoding the tumor protein in a biological sample.

5                   To permit hybridization under assay conditions, oligonucleotide primers and probes should comprise an oligonucleotide sequence that has at least about 60%, preferably at least about 75% and more preferably at least about 90%, identity to a portion of a polynucleotide encoding an ovarian tumor protein that is at least 10 nucleotides, and preferably at least 20 nucleotides, in length. Preferably,  
10 oligonucleotide primers and/or probes hybridize to a polynucleotide encoding a polypeptide described herein under moderately stringent conditions, as defined above. Oligonucleotide primers and/or probes which may be usefully employed in the diagnostic methods described herein preferably are at least 10-40 nucleotides in length. In a preferred embodiment, the oligonucleotide primers comprise at least 10 contiguous  
15 nucleotides, more preferably at least 15 contiguous nucleotides, of a DNA molecule having a sequence recited in SEQ ID NOs:1-1502. Techniques for both PCR based assays and hybridization assays are well known in the art (*see*, for example, Mullis et al., *Cold Spring Harbor Symp. Quant. Biol.*, 51:263, 1987; Erlich ed., *PCR Technology*, Stockton Press, NY, 1989).

20                   One preferred assay employs RT-PCR, in which PCR is applied in conjunction with reverse transcription. Typically, RNA is extracted from a biological sample such as a biopsy tissue and is reverse transcribed to produce cDNA molecules. PCR amplification using at least one specific primer generates a cDNA molecule, which may be separated and visualized using, for example, gel electrophoresis. Amplification  
25 may be performed on biological samples taken from a test patient and from an individual who is not afflicted with a cancer. The amplification reaction may be performed on several dilutions of cDNA spanning two orders of magnitude. A two-fold or greater increase in expression in several dilutions of the test patient sample as compared to the same dilutions of the non-cancerous sample is typically considered  
30 positive.

In another embodiment, ovarian tumor proteins and polynucleotides encoding such proteins may be used as markers for monitoring the progression of cancer. In this embodiment, assays as described above for the diagnosis of a cancer may be performed over time, and the change in the level of reactive polypeptide(s) evaluated. For example, the assays may be performed every 24-72 hours for a period of 6 months to 1 year, and thereafter performed as needed. In general, a cancer is progressing in those patients in whom the level of polypeptide detected by the binding agent increases over time. In contrast, the cancer is not progressing when the level of reactive polypeptide either remains constant or decreases with time.

Certain *in vivo* diagnostic assays may be performed directly on a tumor. One such assay involves contacting tumor cells with a binding agent. The bound binding agent may then be detected directly or indirectly via a reporter group. Such binding agents may also be used in histological applications. Alternatively, polynucleotide probes may be used within such applications.

As noted above, to improve sensitivity, multiple ovarian tumor protein markers may be assayed within a given sample. It will be apparent that binding agents specific for different proteins provided herein may be combined within a single assay. Further, multiple primers or probes may be used concurrently. The selection of tumor protein markers may be based on routine experiments to determine combinations that result in optimal sensitivity. In addition, or alternatively, assays for tumor proteins provided herein may be combined with assays for other known tumor antigens.

#### DIAGNOSTIC KITS

The present invention further provides kits for use within any of the above diagnostic methods. Such kits typically comprise two or more components necessary for performing a diagnostic assay. Components may be compounds, reagents, containers and/or equipment. For example, one container within a kit may contain a monoclonal antibody or fragment thereof that specifically binds to an ovarian tumor protein. Such antibodies or fragments may be provided attached to a support material, as described above. One or more additional containers may enclose elements, such as reagents or buffers, to be used in the assay. Such kits may also, or alternatively, contain



a detection reagent as described above that contains a reporter group suitable for direct or indirect detection of antibody binding.

Alternatively, a kit may be designed to detect the level of mRNA encoding an ovarian tumor protein in a biological sample. Such kits generally comprise  
5 at least one oligonucleotide probe or primer, as described above, that hybridizes to a polynucleotide encoding an ovarian tumor protein. Such an oligonucleotide may be used, for example, within a PCR or hybridization assay. Additional components that may be present within such kits include a second oligonucleotide and/or a diagnostic reagent or container to facilitate the detection of a polynucleotide encoding an ovarian  
10 tumor protein.

The following Examples are offered by way of illustration and not by way of limitation.

## EXAMPLE

Identification of Ovarian Tumor Protein cDNAs

5                    This Example illustrates the identification of cDNA molecules encoding ovarian tumor proteins.

                  Ovarian tumor polynucleotides were isolated by PCR-based subtraction. PolyA mRNA was prepared from ovary metastatic tumor tissues, ovary primary tumor tissues and normal tissues. Three cDNA libraries were constructed, PCR-subtracted  
10                   and analyzed. One library was constructed using a pool of four ovary metastatic omentum mRNAs (referred to herein as ovarian metastatic subtraction library or OvMS library). Two libraries were constructed using a pool of primary ovary tumor mRNAs, including an endometroid adenocarcinoma, a germ cell tumor, a papillary serous adenocarcinoma and a clear cell carcinoma (referred to as primary ovarian tumor  
15                   subtraction libraries or PrOvS1 and PrOvS2). PrOvS1 and PrOvS2 libraries were constructed from different PCR amplified pools from the same initial subtraction. Eight normal tissues were represented in the driver mRNA, including brain, pancreas, bone marrow, lung, heart, kidney, liver and trachea. PolyA mRNA

                  cDNA synthesis, hybridization and PCR amplification were performed  
20                   according to Clontech's user manual (PCR-Select cDNA Subtraction), with the following changes: 1) cDNA was restricted with a mixture of enzymes, including MscI, PvuII, StuI and DraI, instead of the single enzyme RsaI; and 2) the ration of driver to tester cDNA was increased in the hybridization steps (to 76:1) to give a more stringent subtraction. To analyze the efficiency of the subtraction, housekeeping genes such as  
25                   actin and GADPH were PCR amplified from dilutions of subtracted as well as unsubtracted PCR samples. Furthermore, the complexity and redundancy of each library was characterized by sequencing 96 clones from each of the PCR subtraction libraries (OvMS, PrOvS1 and PrOvS2). These analyses indicated that the libraries are enriched for genes overexpressed in ovary tissue and ovary tumor samples.

30                   Following PCR amplification, the cDNAs were cloned into the pCR2,1-TOPO plasmid vector (Invitrogen). 1502 sequences were obtained from the OvMS,

PrOvS1 and PrOvS2 libraries. These sequences are provided herein as SEQ ID NOs:1-1502.

From the foregoing it will be appreciated that, although specific  
5 embodiments of the invention have been described herein for purposes of illustration, various modifications may be made without deviating from the spirit and scope of the invention. Accordingly, the invention is not limited except as by the appended claims.

## CLAIMS

1. An isolated polypeptide comprising at least an immunogenic portion of an ovarian tumor protein, or a variant thereof that differs in one or more substitutions, deletions, additions and/or insertions such that the ability of the variant to react with antigen-specific antisera is not substantially diminished, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence recited in any one of SEQ ID NOs:1-1502.
2. A polypeptide according to claim 1, wherein the polypeptide comprises an amino acid sequence that is encoded by a polynucleotide sequence recited in any one of SEQ ID NOs: 1-1502.
3. An isolated polynucleotide encoding at least 15 amino acid residues of an ovarian tumor protein comprising an amino acid sequence that is encoded by a polynucleotide comprising a sequence recited in any one of SEQ ID NOs:1-1502.
4. A polynucleotide encoding an ovarian tumor protein, or a variant thereof that differs in one or more substitutions, deletions, additions and/or insertions such that the ability of the variant to react with antigen-specific antisera is not substantially diminished, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide comprising a sequence recited in any one of SEQ ID NOs:1-1502.
5. An isolated polynucleotide comprising a sequence recited in any one of SEQ ID NOs:1-1502.
6. An isolated polynucleotide comprising a sequence that hybridizes to a sequence recited in any one of SEQ ID NOs:1-1502, or a complement of any of the foregoing sequences, under moderately stringent conditions.

7. An isolated polynucleotide complementary to a polynucleotide according to any one of claims 3-6.
8. An expression vector comprising a polynucleotide according to any one of claims 3-6.
9. A host cell transformed or transfected with an expression vector according to claim 8.
10. An expression vector comprising a polynucleotide according claim 7.
11. A host cell transformed or transfected with an expression vector according to claim 10.
12. A pharmaceutical composition comprising a polypeptide according to claim 1, in combination with a physiologically acceptable carrier.
13. A vaccine comprising a polypeptide according to claim 1, in combination with a non-specific immune response enhancer.
14. A vaccine according to claim 13, wherein the non-specific immune response enhancer is an adjuvant.
15. A vaccine according to claim 13, wherein the non-specific immune response enhancer induces a predominantly Type I response.
16. A pharmaceutical composition comprising a polynucleotide according to any one of claims 3-6, in combination with a physiologically acceptable carrier.

17. A vaccine comprising a polynucleotide according to any one of claims 3-6, in combination with a non-specific immune response enhancer.

18. A vaccine according to claim 17, wherein the non-specific immune response enhancer is an adjuvant.

19. A vaccine according to claim 17, wherein the non-specific immune response enhancer induces a predominantly Type I response.

20. An isolated antibody, or antigen-binding fragment thereof, that specifically binds to an ovarian tumor protein that comprises an amino acid sequence that is encoded by a polynucleotide sequence recited in any one of SEQ ID NOs:1-1502, or a complement of any of the foregoing sequences.

21. A pharmaceutical composition comprising an antibody or fragment thereof according to claim 20, in combination with a physiologically acceptable carrier.

22. A pharmaceutical composition comprising an antigen-presenting cell that expresses a polypeptide according to claim 1, in combination with a pharmaceutically acceptable carrier or excipient.

23. A pharmaceutical composition according to claim 22, wherein the antigen presenting cell is a dendritic cell or a macrophage.

24. A vaccine comprising an antigen-presenting cell that expresses a polypeptide according to claim 1, in combination with a non-specific immune response enhancer.

25. A vaccine according to claim 24, wherein the non-specific immune response enhancer is an adjuvant.

26. A vaccine according to claim 24, wherein the non-specific immune response enhancer induces a predominantly Type I response.

27. A vaccine according to claim 24, wherein the antigen-presenting cell is a dendritic cell.

28. A method for inhibiting the development of a cancer in a patient, comprising administering to a patient an effective amount of a polypeptide that comprises at least an immunogenic portion of an ovarian tumor protein, or a variant thereof that differs in one or more substitutions, deletions, additions and/or insertions such that the ability of the variant to react with antigen-specific antisera is not substantially diminished, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence recited in any one of SEQ ID NOs:1-1502, or a complement of any of the foregoing sequences, and thereby inhibiting the development of a cancer in the patient.

29. A method for inhibiting the development of a cancer in a patient, comprising administering to a patient an effective amount of a polynucleotide that encodes a polypeptide comprising at least an immunogenic portion of an ovarian tumor protein, or a variant thereof that differs in one or more substitutions, deletions, additions and/or insertions such that the ability of the variant to react with antigen-specific antisera is not substantially diminished, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence recited in any one of SEQ ID NOs:1-1502, or a complement of any of the foregoing sequences, and thereby inhibiting the development of a cancer in the patient.

30. A method for inhibiting the development of a cancer in a patient, comprising administering to a patient an effective amount of an antibody or antigen-binding fragment thereof that specifically binds to an ovarian tumor protein, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide

sequence recited in any one of SEQ ID NOs:1-1502, or a complement of any of the foregoing sequences, and thereby inhibiting the development of a cancer in the patient.

31. A method for inhibiting the development of a cancer in a patient, comprising administering to a patient an effective amount of an antigen-presenting cell that expresses a polypeptide comprising at least an immunogenic portion of an ovarian tumor protein, or a variant thereof that differs in one or more substitutions, deletions, additions and/or insertions such that the ability of the variant to react with antigen-specific antisera is not substantially diminished, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence recited in any one of SEQ ID NOs:1-1502, or a complement of any of the foregoing sequences, and thereby inhibiting the development of a cancer in the patient.

32. A method according to claim 31, wherein the antigen-presenting cell is a dendritic cell.

33. A method according to any one of claims 28-31, wherein the cancer is ovarian cancer.

34. A fusion protein comprising at least one polypeptide according to claim 1.

35. A fusion protein according to claim 34, wherein the fusion protein comprises an expression enhancer that increases expression of the fusion protein in a host cell transfected with a polynucleotide encoding the fusion protein.

36. A fusion protein according to claim 34, wherein the fusion protein comprises a T helper epitope that is not present within the native ovarian tumor protein.



37. A fusion protein according to claim 34, wherein the fusion protein comprises an affinity tag.
38. An isolated polynucleotide encoding a fusion protein according to claim 34.
39. A pharmaceutical composition comprising a fusion protein according to claim 34, in combination with a physiologically acceptable carrier.
40. A vaccine comprising a fusion protein according to claim 34, in combination with a non-specific immune response enhancer.
41. A vaccine according to claim 40, wherein the non-specific immune response enhancer is an adjuvant.
42. A vaccine according to claim 40, wherein the non-specific immune response enhancer induces a predominantly Type I response.
43. A pharmaceutical composition comprising a polynucleotide according to claim 38, in combination with a physiologically acceptable carrier.
44. A vaccine comprising a polynucleotide according to claim 38, in combination with a non-specific immune response enhancer.
45. A vaccine according to claim 44, wherein the non-specific immune response enhancer is an adjuvant.
46. A vaccine according to claim 44, wherein the non-specific immune response enhancer induces a predominantly Type I response.

47. A method for inhibiting the development of a cancer in a patient, comprising administering to a patient an effective amount of a pharmaceutical composition according to claim 39 or claim 43.

48. A method for inhibiting the development of a cancer in a patient, comprising administering to a patient an effective amount of a vaccine according to claim 40 or claim 44.

49. A method for removing tumor cells from a biological sample, comprising contacting a biological sample with T cells that specifically react with an ovarian tumor protein, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence selected from the group consisting of:

(i) polynucleotides recited in any one of SEQ ID NOs:1-1502; and

(ii) complements of the foregoing polynucleotides;

wherein the step of contacting is performed under conditions and for a time sufficient to permit the removal of cells expressing the antigen from the sample.

50. A method according to claim 49, wherein the biological sample is blood or a fraction thereof.

51. A method for inhibiting the development of a cancer in a patient, comprising administering to a patient a biological sample treated according to the method of claim 49.

52. A method for stimulating and/or expanding T cells specific for an ovarian tumor protein, comprising contacting T cells with one or more of:

(i) a polypeptide that comprises at least an immunogenic portion of an ovarian tumor protein, or a variant thereof that differs in one or more substitutions, deletions, additions and/or insertions such that the ability of the variant to react with antigen-specific antisera is not substantially diminished, wherein the tumor protein

comprises an amino acid sequence that is encoded by a polynucleotide sequence recited in any one of SEQ ID NOs:1-1502, or a complement of any of the foregoing sequences;

(ii) a polynucleotide encoding such a polypeptide; and/or

(iii) an antigen presenting cell that expresses such a polypeptide;

under conditions and for a time sufficient to permit the stimulation and/or expansion of T cells.

53. An isolated T cell population, comprising T cells prepared according to the method of claim 52.

54. A method for inhibiting the development of a cancer in a patient, comprising administering to a patient an effective amount of a T cell population according to claim 53.

55. A method for inhibiting the development of a cancer in a patient, comprising the steps of:

(a) incubating CD4<sup>+</sup> and/or CD8<sup>+</sup> T cells isolated from a patient with at least one component selected from the group consisting of:

(i) a polypeptide that comprises at least an immunogenic portion of an ovarian tumor protein, or a variant thereof that differs in one or more substitutions, deletions, additions and/or insertions such that the ability of the variant to react with antigen-specific antisera is not substantially diminished, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence recited in any one of SEQ ID NOs:1-1502, or a complement of any of the foregoing sequences;

(ii) a polynucleotide encoding such a polypeptide; and

(iii) an antigen-presenting cell that expresses such a polypeptide, such that T cells proliferate; and

(b) administering to the patient an effective amount of the proliferated T cells, and thereby inhibiting the development of a cancer in the patient.

56. A method for inhibiting the development of a cancer in a patient, comprising the steps of:

(a) incubating CD4<sup>+</sup> and/or CD8<sup>+</sup> T cells isolated from a patient with at least one component selected from the group consisting of:

(i) a polypeptide that comprises at least an immunogenic portion of an ovarian tumor protein, or a variant thereof that differs in one or more substitutions, deletions, additions and/or insertions such that the ability of the variant to react with antigen-specific antisera is not substantially diminished, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence recited in any one of SEQ ID NOs:1-1502, or a complement of any of the foregoing sequences;

(ii) a polynucleotide encoding such a polypeptide; and

(iii) an antigen-presenting cell that expresses such a polypeptide; such that T cells proliferate;

(b) cloning at least one proliferated cell; and

(c) administering to the patient an effective amount of the cloned T cells, and thereby inhibiting the development of a cancer in the patient.

57. A method for determining the presence or absence of a cancer in a patient, comprising the steps of:

(a) contacting a biological sample obtained from a patient with a binding agent that binds to an ovarian tumor protein, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence selected from the group consisting of:

(i) polynucleotides recited in any one of SEQ ID NOs:1-1502; and

(ii) complements of the foregoing polynucleotides;

(b) detecting in the sample an amount of polypeptide that binds to the binding agent; and

(c) comparing the amount of polypeptide to a predetermined cut-off value, and therefrom determining the presence or absence of a cancer in the patient.

58. A method according to claim 57, wherein the binding agent is an antibody.

59. A method according to claim 58, wherein the antibody is a monoclonal antibody.

60. A method according to claim 57, wherein the cancer is ovarian cancer.

61. A method for monitoring the progression of a cancer in a patient, comprising the steps of:

(a) contacting a biological sample obtained from a patient at a first point in time with a binding agent that binds to an ovarian tumor protein, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence recited in any one of SEQ ID NOs:1-1502 or a complement of any of the foregoing polynucleotides;

(b) detecting in the sample an amount of polypeptide that binds to the binding agent;

(c) repeating steps (a) and (b) using a biological sample obtained from the patient at a subsequent point in time; and

(d) comparing the amount of polypeptide detected in step (c) to the amount detected in step (b) and therefrom monitoring the progression of the cancer in the patient.

62. A method according to claim 61, wherein the binding agent is an antibody.

63. A method according to claim 62, wherein the antibody is a monoclonal antibody.

64. A method according to claim 61, wherein the cancer is ovarian cancer.

65. A method for determining the presence or absence of a cancer in a patient, comprising the steps of:

(a) contacting a biological sample obtained from a patient with an oligonucleotide that hybridizes to a polynucleotide that encodes an ovarian tumor protein, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence recited in any one of SEQ ID NOs:1-1502 or a complement of any of the foregoing polynucleotides;

(b) detecting in the sample an amount of a polynucleotide that hybridizes to the oligonucleotide; and

(c) comparing the amount of polynucleotide that hybridizes to the oligonucleotide to a predetermined cut-off value, and therefrom determining the presence or absence of a cancer in the patient.

66. A method according to claim 65, wherein the amount of polynucleotide that hybridizes to the oligonucleotide is determined using a polymerase chain reaction.

67. A method according to claim 65, wherein the amount of polynucleotide that hybridizes to the oligonucleotide is determined using a hybridization assay.

68. A method for monitoring the progression of a cancer in a patient, comprising the steps of:

(a) contacting a biological sample obtained from a patient with an oligonucleotide that hybridizes to a polynucleotide that encodes an ovarian tumor protein, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence recited in any one of SEQ ID NOs:1-1502 or a complement of any of the foregoing polynucleotides;

(b) detecting in the sample an amount of a polynucleotide that hybridizes to the oligonucleotide;

(c) repeating steps (a) and (b) using a biological sample obtained from the patient at a subsequent point in time; and

(d) comparing the amount of polynucleotide detected in step (c) to the amount detected in step (b) and therefrom monitoring the progression of the cancer in the patient.

69. A method according to claim 68, wherein the amount of polynucleotide that hybridizes to the oligonucleotide is determined using a polymerase chain reaction.

70. A method according to claim 68, wherein the amount of polynucleotide that hybridizes to the oligonucleotide is determined using a hybridization assay.

71. A diagnostic kit, comprising:

(a) one or more antibodies according to claim 20; and

(b) a detection reagent comprising a reporter group.

72. A kit according to claim 71, wherein the antibodies are immobilized on a solid support.

73. A kit according to claim 72, wherein the solid support comprises nitrocellulose, latex or a plastic material.

74. A kit according to claim 71, wherein the detection reagent comprises an anti-immunoglobulin, protein G, protein A or lectin.

75. A kit according to claim 71, wherein the reporter group is selected from the group consisting of radioisotopes, fluorescent groups, luminescent groups, enzymes, biotin and dye particles.

76. An oligonucleotide comprising 10 to 40 nucleotides that hybridize under moderately stringent conditions to a polynucleotide that encodes an ovarian tumor protein, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence recited in any one of SEQ ID NOs: 1-1502, or a complement of any of the foregoing polynucleotides.

77. A oligonucleotide according to claim 76, wherein the oligonucleotide comprises 10-40 nucleotides recited in any one of SEQ ID NOs: 1-1502.

78. A diagnostic kit, comprising:  
(a) an oligonucleotide according to claim 76; and  
(b) a diagnostic reagent for use in a polymerase chain reaction or hybridization assay.



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540cttggaaaaan ggcttttaat cctagaatct tttttccanc canattgcct tttgatttan  
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658

<210> 15<211> 713<212> DNA<213> Homo sapiens

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120gagatacaaa gaaagtaact ctccctctta tgaaaagcaa ccaggaaactc tactccagtt  
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360tgtagaaaaat caaagtgaat gggaatgtgg tgggtgtgaac ataaaagaag aaattgaaaa  
420caatcaaaaag tttctcagtg ctgctttccc gcaactgtcat agaaatctct gatccaattc  
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600gggaaatcct tatactcccc tccgncgg ggctaattnc cattggtgaa acaatgttgg  
660gggggaaaaa aggttttgct cctacctana ngaaccagag ggcttgttcc ccc

713

&lt;210&gt; 16&lt;211&gt; 616&lt;212&gt; DNA&lt;213&gt; Homo sapiens

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60tacataaaac tagcagcaaa aagtatctag aaatctgtcg tgtgcaaata gttttcttcc  
120caactatcat tcccatggtc ccaaataaat tttagaatct agtcccatcc ccttcctaga  
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480agcggttttg taaccgcatt ctggacctcg ggccgcgacc cacgctaagg gcgaaattnc  
540agcaccctt ngcggggcgn ttntagtgg gatcccaact cggtagccaa acnttggcgt  
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616

&lt;210&gt; 17&lt;211&gt; 753&lt;212&gt; DNA&lt;213&gt; Homo sapiens

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180cacacgcctt cacttaaaaa ggccgaggag cggcgggatc cacctgaatc caattacatc  
240tggtgaactc cgacatctga aacgttttaa gttacaccaa gttcatagcc tttgttaacc  
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600tggcgtaagt cacaaaaaat tggaatggtg caagttaatt gttgaaagta cancaatttc  
660anattttatt gcananattt agangttggt tacattttta cttggccgga acacctaang  
720gcgnaatnca cacactggng gcngtatang ggn  
753

&lt;210&gt; 18&lt;211&gt; 148&lt;212&gt; DNA&lt;213&gt; Homo sapiens

ggcaggtaaa gtaagtcgtt tccttttatt tgaacaccta ggggccattt tagagttata  
60attagcccaa tttctatata attttgtctc agggaataga agcgtgaggg agggagagag  
120ttgggggaat ggctggttg tagagtgg  
148

&lt;210&gt; 19&lt;211&gt; 262&lt;212&gt; DNA&lt;213&gt; Homo sapiens

agcggccgcc cgggcaggtg aaagacctca agaaagcaac gaaaggaacg caagaacaga  
60atgaagaaag tcagggggac tgcaaaggcc aatgttggtg ctggcaaaaa gccgaaggag  
120taaagggtgct gcaatgatgt tagctgtgga cctcgccgc gaccacgcta aggcgaatt  
180ccagcacact ggccggcgtt actagtggat ccgagctcgg taccaagctt ggcgtaatca  
240tggtcatagc tgtttcctgt ga  
262

&lt;210&gt; 20&lt;211&gt; 451&lt;212&gt; DNA&lt;213&gt; Homo sapiens

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120aaatgacaaa gaggcagcag gagaggccc agccctgtat gaggacccc cagatcagaa  
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240tcgagcctgg attaagaaga aaggattaga ttgggtaaag gaagaagccc cagatatact  
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360taaggggcgaa ttccagcaca ctgcggcgt tactagtga tccgagctcg gtaccaagct  
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451

&lt;210&gt; 21&lt;211&gt; 698&lt;212&gt; DNA&lt;213&gt; Homo sapiens

ctgttgaaat gaagcacttt acagtctttg tggcagcaga atatacttgt ccatgggttca  
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 120tgagggggga gggggtgggg aaaagaagga aaaaaaggga aaaacaacca aaataattta  
 180agtaaatgac agattggaaa acagggttta taaaaattat tctcttgagt ttataaattg  
 240ttaaactcaa tttatagcta tgttaaacta cgtaagaacc actatactga aagaccattt  
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 360acctaaagaa gtttaactga agcttagaac tattttgctc tacaccctca gctttcgttg  
 420gnatccttat aaactactgt attaaagggt ttgtagaaac agcacagttn ttaaagactg  
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 540cctcgctggg gttatttcct ttccttnntt tgaaaaancc agctttttaa aaatttaaaa  
 600ggggttttctt ctngcagana tncctntaag tanccaentn ccttatcctg agaanggcna  
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 698

<210> 22<211> 58<212> DNA<213> Homo sapiens

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<210> 23<211> 446<212> DNA<213> Homo sapiens

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 120atgctgctaa aaacaagact ggggctgctc ccatcattga tgtggtgcca tggggtact  
 180acaaagtctt gggaaaggga aagctcccaa agcagcctgt catcgtgaag gccaaattct  
 240tcagcagaag agctgaggag aagattaaga gtgttggggg ggcctgtgtc ctggtggctt  
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<210> 24<211> 401<212> DNA<213> Homo sapiens

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 240gtggggagaca agtggatctg gctgaagtga acgggccgcc ttctgctcca gacctgccc  
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 401

<210> 25<211> 615<212> DNA<213> Homo sapiens

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 120tcaagatcag taaattttag aaaagcttca gagtctttga aaggaaacat ggctgctttt  
 180ctaaagaatg tgtgtctggg gttggaagat ctgcagtatg ttttcatgat ttcttcacat  
 240gagcttttca ttacattgtt gaaagatgaa gaacgaaagc tacttggtga tcagatgagg  
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 420tgaggagatta gacaaatttt aattgaatta catggtatga cttcagaacg ccagttctgg  
 480acagtgtcta ataagtggga agtaccttct gtctatagtg gtgttatcct gggaattaaa  
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 615

<210> 26<211> 714<212> DNA<213> Homo sapiens

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 120gagcaaaaa gagcaagaaa caaaaagaag caaaagcag aaggctccaa tatgaacaag  
 180ataaatctat cttcaaagac atattagaag ttgggaaaat aattcatgtg aactagacaa

240gtgtgtttaag agtgataagt aaaatgcacg tggagacaag tgcattccca gatctcaggg  
 300acctccccct gcctgtcacc tggggagtga gaggacagga tagtgcatgt tctttgtctc  
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 600gagaaaaatg atcntatatt acnttaccna cagcngggac ccctttttta ataactggca  
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<210> 27<211> 512<212> DNA<213> Homo sapiens

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 120atactttgtc ttagccca ca ctgcaaat ac agcactatta tggcatctta atcaagcaga  
 180gagctgttca catgctttct acagtatctt tataaataaa aggttccttt atccaccaa  
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 360ttgtaaattt agtcaacata cataattgac ctaaaaactt cagtaaattt tacctcggn  
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<210> 28<211> 547<212> DNA<213> Homo sapiens

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 180gtaatagaat agcacagcca gacttgcttc ctgcatggta gggagagaca caaaagatgg  
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 420tatatttttg gtactggagc ttttacctgc ccggcgccg gcttcaaagg gcgaattcca  
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<210> 29<211> 273<212> DNA<213> Homo sapiens

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 273

<210> 30<211> 178<212> DNA<213> Homo sapiens

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 178

<210> 31<211> 698<212> DNA<213> Homo sapiens

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 180taaaaaataa aaagaaaata cagcataata aaaaacatac gcttctcaat taaatgtact  
 240ggatacatat aaattttaag ggaagaagca aaaaaggaaa atgattgata ttaagtgc  
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698

<210> 32<211> 274<212> DNA<213> Homo sapiens

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274

<210> 33<211> 381<212> DNA<213> Homo sapiens

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120gtgtgantcn ntaatataaa tgcggagacg taaagcatta atgcaagtta aaatgtttca  
180gagaacaant ttcagcgggt cactttataa taattataaa taaacctgtt aaatttttct  
240ggacaatgcc agcatttgga tttttttacc tgcccggggc ggccgctcaa aagggcgaat  
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381

<210> 34<211> 457<212> DNA<213> Homo sapiens

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457

<210> 35<211> 732<212> DNA<213> Homo sapiens

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732

<210> 36<211> 232<212> DNA<213> Homo sapiens

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120cctcggccgc gaccacgcta agggcgaatt ccagcacact ggccggccgtt actagtggat  
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232

<210> 37<211> 448<212> DNA<213> Homo sapiens

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180cccgcgtgcat tcccctatgg gtcggagccc ggggcattga gtttgactgg aagtacatcc  
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448

<210> 38<211> 549<212> DNA<213> Homo sapiens

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549

<210> 39<211> 474<212> DNA<213> Homo sapiens

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474

<210> 40<211> 395<212> DNA<213> Homo sapiens

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395

<210> 41<211> 682<212> DNA<213> Homo sapiens

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682

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120ggagtacagt ggcgcgatct tagctcaccg caacctccgc ctcccgggtt caagcgattc  
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240ttttttatgn ttaggcagat ggggnttcnc catgctggtc cgggctggct tgangccnt  
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240acaagacata tatataaaat nctctgaatg tgcaataaaa ngaagtnctt tgttaaaaag  
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120acttccaaca tactagcggc caaactaccg aataaacttg atgcagacca gtattcccaa  
180gttgcaatag tatccaatga ctttgctgaa atgcataaaa tggacaagcc taggtatctg  
240cgcaaccagc aggttttttt tttgtnccaa ggctngagaa tgcttggtta agcttgcca  
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457

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120caatgtagaa ctacgccttc ttggaaagaa aaaaaagagg ctccgggttg acaaatggtg  
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245

<210> 46<211> 381<212> DNA<213> Homo sapiens  
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120ggatattaga agtaagaaaa gtacaaaaga ngtttgctta gaaataacaa aaaattaaaa  
180aaaaaaaaan ggatcccccn tcccccaat cccnataatc ggggnntagc caaccatcgg  
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381

<210> 47<211> 364<212> DNA<213> Homo sapiens  
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120agaccagcaa tgtaacttta ttttngcatt nattnaattg aaaatataaa caataattaa  
180aaaataaaaa gaaaatacag cataataaaa aacatacgt tctcaattaa atgtactgga  
240tacatataaa ttttaaggga anaagcnaaa aangaaaatg attgatnttt aagtgcagac  
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360tttg

364

<210> 48<211> 496<212> DNA<213> Homo sapiens  
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120acggatgaaa atattcaaga aggcttagct cccaagcctc cccctccaat aaaagacagt  
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240cagggcatcg aacggcttca tcctatgcag ttgatcaca agaaagaact gacaaaactt  
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496

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397

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agaccgacga 60ggaggaggat tnagtccact tgnnctctg gg  
92

<210> 51<211> 316<212> DNA<213> Homo sapiens  
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120ccttcagata ccaaggaaatg actgtacatg ttggtagaa aactagttgt ctctacctag  
180tctccattct ggtcacttct ttagtttctt aatttcagag taaggccant ctcttctgt  
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300tttttncacg tngtgt  
316

<210> 52<211> 541<212> DNA<213> Homo sapiens  
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120cagaactctt gtctgcata tcatcgattt gcacaccctg gaacaacgtt tggtagaaat  
180caacttggga aatgttgac agcatgagt atgaatacag ctaagttagg atcaaagtac  
240aggcgtatct cgttttactg cacttcactt tactgagctt catagatatt gtgcttttac  
300aaattgcacg tctgtagcat cctccttga caantctatt ggtgncattt ttccaagagg  
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420cattattatt ttatcttgtt ccggtgacct gngggcangc gagcttttat gtnactatng  
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540g  
541

<210> 53<211> 321<212> DNA<213> Homo sapiens  
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120tctccgcatt tatattaaaa attcacacac aaatgaaaat ggaaaaactg ccaataacctg  
180attttctgncc cctatttttc cactcgcaat catntactta ngtaaccttt gaccccatgg  
240aaaaaaaaann ttaaccgttc aggactnccc attaccggaa gaaaaaaaat tttttttttt  
300ttggnaaaaa aaaaagtcc c

321

&lt;210&gt; 54&lt;211&gt; 547&lt;212&gt; DNA&lt;213&gt; Homo sapiens

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60ttaactgcac catccaaatt cttgtgactt acgcattttt gcccaattta acctttctga  
120tgttcccctg cccccagaca ccataaatgc attgtaattt tgaaaatata tgccaactac  
180aactgaaaa ttttaacctg atcaattgac ataataaaa atctgtccca aagcactgaa  
240acaagaaaat ctataccatc atgctacaga cgtacttaga aaacttaaaa ggaagaagta  
300aatatcagct cagtgtttta tnatgaagct aataaaattc aaggccagta ttcttaagt  
360taatgaacat tatttgaaca ttcacacatg aaanggtaac aaagggtat gaacttggg  
420taacttttaa acgtttcaga tgtccggagt tcaccanag taattggatt caggtgggat  
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540gcctcag  
547

&lt;210&gt; 55&lt;211&gt; 439&lt;212&gt; DNA&lt;213&gt; Homo sapiens

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60cctctgaatt ttactgatga agaaactgag gccacagagc taaagtgact tttcccaagg  
120tcgcccagcg aggacgtggg acttctcaga cgtcaggaga gtgatgtgag ggagctgtgt  
180gaccatagaa agtgacgtgt taaaaaccag cgctgccctc ttgaaagcc agggagcatc  
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360acancgnang aagaagtgtt gtngatggag cngacgtccc taatgtccgg cttgagagcc  
420ccacncccg ctcctgcc  
439

&lt;210&gt; 56&lt;211&gt; 442&lt;212&gt; DNA&lt;213&gt; Homo sapiens

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120agtttttattt atttattttc ttttttgaca tggagtctcg ctctgtcgcc caggctggag  
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442

&lt;210&gt; 57&lt;211&gt; 432&lt;212&gt; DNA&lt;213&gt; Homo sapiens

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60agacggggat gagctcagga cagagccaga ggccaagaag agtaagacgg ccgcaaagaa  
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300gtgccttcaa ganaccaatg ttcngagaca aactccagac ctcgcccgcg acacctaaag  
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420actgtttctt ga  
432

&lt;210&gt; 58&lt;211&gt; 217&lt;212&gt; DNA&lt;213&gt; Homo sapiens

aaaatcctga ttttgagac ttaaaaccag gtaatggct aagaatgggt aacatgactc  
60ttgttggatt gttatttttt gttgcaatg gggaatttat aagaagcatc aagtctcttt  
120cttaacaaaag tcttgttagg tggtttatag ttcttttggc taacaaatca ttttggaat  
180aaagattttt ttactacaaa aaaaaaaaaa aaaatat  
217

&lt;210&gt; 59&lt;211&gt; 566&lt;212&gt; DNA&lt;213&gt; Homo sapiens

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 480caccgnggg gtgntgtccc aagaagaaaa taagnctttt aggacctccc ngggcggggc  
 540ttngaaagg ngatttncag gccact  
 566

<210> 60<211> 234<212> DNA<213> Homo sapiens

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 120ctagtttctc cgtccctaca caggagctc ctcccaagg gtagatcgga ccgttcatgc  
 180tgccatagga cattatgtcc ctcaaaaaaa aaaactcctt ngcctgcac cgtg  
 234

<210> 61<211> 385<212> DNA<213> Homo sapiens

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 385

<210> 62<211> 455<212> DNA<213> Homo sapiens

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 455

<210> 63<211> 570<212> DNA<213> Homo sapiens

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 570

<210> 64<211> 105<212> DNA<213> Homo sapiens

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105

<210> 65<211> 427<212> DNA<213> Homo sapiens

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240cgttccccgt ggaccttatt gtctcttgtg cggatattaa cagngccact gattttctct  
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427

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120tatggtgtgt taataacaat aagaaactta gggaagcagg ctgtggactt ctggaattac  
180caacaggaat gaggaagaa gaaaactgga gtttccagtc tctgagttct acctgatga  
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471

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357

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395

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120tggttcattg acgattgcat tggtaactgg tggagaccaa attttgaacc tctcagtat  
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363

<210> 70<211> 269<212> DNA<213> Homo sapiens  
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180ttgaacgtgn agtggaccac aatgnnctga atgggctgnt ctaccanatn tttctttag  
240ggcnacantc acnnggcggc caaatgtgg  
269

<210> 71<211> 546<212> DNA<213> Homo sapiens  
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<210> 73<211> 527<212> DNA<213> Homo sapiens

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 240tctttgcttt atatacataa gcgcatctct tgcccaaata gaattctgtt tcatctcggg  
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 420ttcccacang actgccgggc ggccgtcgaa nggcnaattc cacacacttn gggcggtct  
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<210> 74<211> 557<212> DNA<213> Homo sapiens

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 420tcaagttcag gtttagaaaa gggagtctgt tccagatcaa tnccnaact gtgcccangc  
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<210> 75<211> 562<212> DNA<213> Homo sapiens

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540ctcggnncca agcttggggg ta  
562

<210> 76<211> 451<212> DNA<213> Homo sapiens  
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240acctttcatg tgttgaatgt tcaaataatg ttcattacac ttaagaatac tggcctgaat  
300tttattaact tctnattaaa tcaattgagc tgatattact cttcctttta agttttctaa  
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5451

<210> 77<211> 252<212> DNA<213> Homo sapiens  
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120ccaccgcatg tagcacacct gccggggcgg ccgctcgaaa gggcgaattc cagcacactg  
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240gtttcctgtg at  
252

<210> 78<211> 546<212> DNA<213> Homo sapiens  
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120tggaactat ttt cagtttaata tacagtaata cactgtagat aaagttaata tccccccac  
180taatttaata gggattgata tcaatgtttc tgatcactgg agaaataaaa actaatgtgg  
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360aaaancagng gtttggaata aaaaantaat caaaacccat aatcacatct cttgtggata  
420acaatattaa tataactttt taccaccca ngacttgct gtncaaactc agaactgaaa  
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546

<210> 79<211> 545<212> DNA<213> Homo sapiens  
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120ctaagtttaa tagtcatctc ctctgctgac aacttcttta catgttgga gcaacaggat  
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360aagtgttttg ttcttggaag ccttattggg cacatgtcca acatcaaaat tttcatgta  
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545

<210> 80<211> 559<212> DNA<213> Homo sapiens  
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120cctcctctgg gaaatagagg agtgatattg ttagtaccta gggcatagca ctgctgggac  
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420attcntagga cctcgggccc cnaccacnct taangggcnn aattcccagn ccacctgggc  
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559

<210> 81<211> 515<212> DNA<213> Homo sapiens  
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300aagagatccc cttgagtaaa tctgtgcatt aaccngnaac ttcatttnat gatatcccca  
360gctcagcaag gagtcaacan tgggcagtta gaagcatcaa ctnatattgg ccagtgggat  
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515

<210> 82<211> 305<212> DNA<213> Homo sapiens  
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180aaaaatttat ttacctgcc gggcgccgc taaggcgaa ttccagcaca ctggcgccgc  
240ttactantgg atccganctc ggtaccaagc ttggcgtaat catggtcata gctgtttcct  
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305

<210> 83<211> 572<212> DNA<213> Homo sapiens  
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360tgaaggctcg agtgagttct tcagggaagc gatactcttg agtaccacag ggaccagccg  
420tccttatcaa agtgcctcca gaaatatggc agtgccacag agagtgnctc ctcatggag  
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572

<210> 84<211> 588<212> DNA<213> Homo sapiens  
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360aattttccat aagctatttt ggtttantgc aaagtataaa attatatttg gggggggaat  
420aagaatatat ggactttctt gcaagcnaca agctattttt tacctgcccc gggcgggccg  
480ctcgaaaggg ccgaantcca agaccacttg gcggcccggt actagtnnga tcccaactcg  
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588

<210> 85<211> 496<212> DNA<213> Homo sapiens  
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420aattccacac actgngggcgg tactatggat ccaactcgga ccaacttggc gtaatcatgg  
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496

<210> 86<211> 335<212> DNA<213> Homo sapiens

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120agttttcatga ctcaatttca tcaaaaatct cagcagcttc atcctagcgg cgcggtcacc  
180ctctgggtcc gacagcacac agaatccttc aaccgaacac tgacacctgc ccgggcggcc  
240gctaagggcg aattccagca cactggcggc cgttactagt ggatccgagc tcggtaccaa  
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335

<210> 87<211> 596<212> DNA<213> Homo sapiens

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120gaaagaatca acggaagact acaatgtggc ctgcaccta accctgcctc cctaccagcg  
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360gatcaccatc aatgagatta gtgaaatcac cagcatcaag aangaggatg tcatctccac  
420tctgcagtac ctcaatctca tcaactacta caanggccag tacatcctca cactgtcaga  
480agacatcgtg gatggacctc gngcgcgaac accttaaggg cgaattccac acacttggcg  
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596

<210> 88<211> 114<212> DNA<213> Homo sapiens

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60aactttttat gtatagcttc taaaagggga aaaaaaaaaa aanaaaaccc nttt

114

<210> 89<211> 609<212> DNA<213> Homo sapiens

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120cacctgccat acatggatct ggatctggat cttgtcagtg actttatgag agtttctgcc  
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480tttaagaacc aagtctaang aacatttttag tggaccttgc ccgggcggcc cctaangcga  
540aattccaccn cacttgnngc ngtncttan gatccaactt cggnccaact tggcgtaac  
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609

<210> 90<211> 594<212> DNA<213> Homo sapiens

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180ccataccagg gaattttttt aacacacagt gttagcctt tgccagagat gttgaaaggg  
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594

<210> 91<211> 465<212> DNA<213> Homo sapiens

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120agaaaatcaa aagaggaata tgaccaggaa gaagaaagga agaggaaaaa acagttatca  
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360aaangacctc ggccgcgacc acgctaang cgaattccac acactggcgg cggttcta  
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465

<210> 92<211> 538<212> DNA<213> Homo sapiens

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538

<210> 93<211> 537<212> DNA<213> Homo sapiens

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120tctcccaaaa ttataaacag ccataccttg gaagcangca gagttaagac gtctcccaac  
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240tgcatcttcat gaggagaaac tgggtacaaa atatgggtgg ggagtcgggg ggtgtgagaa  
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420tttttgcct tgttctctcc cnaagagctc tctcactan acacaaactc tttgctcttg  
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537

<210> 94<211> 417<212> DNA<213> Homo sapiens

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300actttgggta octatgtacc tgttaccact ttcaaaaatc tacagacagt caatgtggat  
360gagaactaat cgctgatcgt canatcaaat aaagttataa aattgcaatt tttttt  
417

<210> 95<211> 560<212> DNA<213> Homo sapiens

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420ncaaaaacac naaaatggaa tgaagtgata ctcttcacat aacagaagtg actgttatct  
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560

<210> 96<211> 618<212> DNA<213> Homo sapiens

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120ttcacctatt accatcaggt tgcttatttt tgttttatgt tttttatttg tatgcatggt  
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300ataaaaacat tttattcaca aaattgggtc tcacagcatt atttacaata ctgaaaatct  
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480agtaaaaaag aacataaatt acatgataaa gaatatgatc agaacaatgc aaaaaattcc  
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618

<210> 97<211> 452<212> DNA<213> Homo sapiens

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452

<210> 98<211> 591<212> DNA<213> Homo sapiens

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591

<210> 99<211> 103<212> DNA<213> Homo sapiens

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103

<210> 100<211> 516<212> DNA<213> Homo sapiens

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516

<210> 101<211> 380<212> DNA<213> Homo sapiens

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380

<210> 102<211> 589<212> DNA<213> Homo sapiens

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480gagactaaga ccatggcaaa agttttacca ccgtctgaag tccctgatga tcagactnag  
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589

<210> 103<211> 209<212> DNA<213> Homo sapiens

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120ntagggcctt tccngcaang gaccaggagg cctcaggccc cccaaagctt aggttagcaa  
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209

<210> 104<211> 665<212> DNA<213> Homo sapiens

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240tttaaggaca cgcacacaag acatatatat aaaattctct gaatgtgcaa taaaagaagt  
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665

<210> 105<211> 466<212> DNA<213> Homo sapiens

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466

<210> 106<211> 355<212> DNA<213> Homo sapiens

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120caaaagttgg agggagcgcc ccangagaac aaacagcaag ccttatttcc cctagcccat  
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240cattccttcc caaattatgg aagtaagggt cttctacca gaataagagc acttgggata  
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355

<210> 107<211> 742<212> DNA<213> Homo sapiens  
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180ggaagcataa agtgtaaagc ctgggggtgc taatgagtga gctaactcac attaatgctg  
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<210> 108<211> 461<212> DNA<213> Homo sapiens  
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461

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285

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623

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638

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595

<210> 113<211> 598<212> DNA<213> Homo sapiens  
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598

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489

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244

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465

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561

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479

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638

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446

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559

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<210> 122<211> 576<212> DNA<213> Homo sapiens

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576

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<210> 124<211> 483<212> DNA<213> Homo sapiens

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<210> 125<211> 737<212> DNA<213> Homo sapiens

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<210> 126<211> 555<212> DNA<213> Homo sapiens

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<210> 127<211> 403<212> DNA<213> Homo sapiens

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<210> 128<211> 727<212> DNA<213> Homo sapiens

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<210> 131<211> 534<212> DNA<213> Homo sapiens

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<210> 132<211> 539<212> DNA<213> Homo sapiens

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<210> 133<211> 531<212> DNA<213> Homo sapiens

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531

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534

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499

<210> 136<211> 529<212> DNA<213> Homo sapiens

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420cggtcagccc tgccctcggg aactgctggg gaggtgggat ggggtcaggg agtggacctc  
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<210> 137<211> 449<212> DNA<213> Homo sapiens

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536

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<210> 140<211> 532<212> DNA<213> Homo sapiens

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532

<210> 141<211> 535<212> DNA<213> Homo sapiens

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535

<210> 142<211> 551<212> DNA<213> Homo sapiens

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<210> 143<211> 533<212> DNA<213> Homo sapiens

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533

<210> 144<211> 491<212> DNA<213> Homo sapiens

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180atTTtgatc tatcacctgt catcataact ggcttctgt tTcatccac acaacaccag  
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180gcctTTtaag ttactgacat cagcttcac cagtTtaaaa attgagTaaa acctgaagTt  
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 360ctagtnnggat ccgagctcgg naccaagctt ggcttnatca tggatcatagn tnnnttctct  
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<210> 155<211> 537<212> DNA<213> Homo sapiens

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104

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109

<210> 163<211> 529<212> DNA<213> Homo sapiens

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529

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453

<210> 166<211> 534<212> DNA<213> Homo sapiens

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534

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439

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558

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533

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636

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93

<210> 177<211> 479<212> DNA<213> Homo sapiens

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479

<210> 178<211> 315<212> DNA<213> Homo sapiens

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120aaaangangn aaaaaganag atttcattaa tagnnocctt tnaaactcca aatnntctg  
 180cattttaagcn catncaatca ggtaccttaa agangacat ttttggtctt tgcaatttgt  
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<210> 179<211> 625<212> DNA<213> Homo sapiens

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<210> 181<211> 446<212> DNA<213> Homo sapiens

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<210> 182<211> 419<212> DNA<213> Homo sapiens

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 419

<210> 183<211> 307<212> DNA<213> Homo sapiens

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120ctgggtgtag aaacatgctt gccttatgta tcanaggaca tgctcagcng atccaagaga  
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 307

<210> 184<211> 465<212> DNA<213> Homo sapiens  
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 469

<210> 186<211> 518<212> DNA<213> Homo sapiens  
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 240ccaaagcact gaaacaagaa aatctatacc atcatgctac agacgtactt agaaaaacta  
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<210> 189<211> 600<212> DNA<213> Homo sapiens  
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 420caagtacacc tgaaatacac cnnngtttac ctgccctggc gggcgctcta aaggcggaan  
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 180gaatanagt ngccccaaa tggaaaanta cacattattt tgtttcaaaa agcnataaat  
 240ttantgcttg aaaaatccan caggttaagca tnaaggacta acagggtctg ttcttggaac  
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 341

<210> 193<211> 381<212> DNA<213> Homo sapiens  
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381

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36

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120gcattnccta gacaaa  
136

<210> 196<211> 553<212> DNA<213> Homo sapiens  
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120aaccaaaaca tttctgggat atgtgactta aggaataaaa aaactcangt gttttataaa  
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300aatataagta ttttcaactg ntacaatact tgaggagatt tttcggccta atttctcaga  
360aactcgccna aagaatagct attctttaca cagaatanct taaaaatttc catgnggaag  
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553

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180agnacc  
186

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180aaganaaaat cagttcgtgg ntgcnttggt gatgcaaact tgancgttct caacttggtt  
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299

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598

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440

<210> 201<211> 621<212> DNA<213> Homo sapiens

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621

<210> 202<211> 628<212> DNA<213> Homo sapiens

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628

<210> 203<211> 515<212> DNA<213> Homo sapiens

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515

<210> 204<211> 269<212> DNA<213> Homo sapiens

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180agtttgcaata gtatncaatg actttgctga aatgcataaa atggacaagc ctatgtatct  
240gcgcaaccan caggtttttt tttattttta  
269

<210> 205<211> 179<212> DNA<213> Homo sapiens

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179

<210> 206<211> 187<212> DNA<213> Homo sapiens

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187

<210> 207<211> 98<212> DNA<213> Homo sapiens

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98

<210> 208<211> 180<212> DNA<213> Homo sapiens

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180

<210> 209<211> 626<212> DNA<213> Homo sapiens

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<210> 210<211> 426<212> DNA<213> Homo sapiens

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<210> 211<211> 81<212> DNA<213> Homo sapiens

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81

<210> 212<211> 115<212> DNA<213> Homo sapiens

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318

<210> 214<211> 274<212> DNA<213> Homo sapiens  
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274

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153

<210> 217<211> 150<212> DNA<213> Homo sapiens  
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150

<210> 218<211> 228<212> DNA<213> Homo sapiens  
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120ttatnaccc ttttncnttc cccctgcac aatgaatacc cngtctctt nncatgccc  
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228

<210> 219<211> 505<212> DNA<213> Homo sapiens  
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505

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503

<210> 221<211> 606<212> DNA<213> Homo sapiens

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606

<210> 222<211> 584<212> DNA<213> Homo sapiens

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584

<210> 223<211> 419<212> DNA<213> Homo sapiens

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419

<210> 224<211> 432<212> DNA<213> Homo sapiens

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549

<210> 226<211> 747<212> DNA<213> Homo sapiens

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540aaatattttt ggggactttt gaaaaaana attccnctn aaanaagatg ttccaaatg  
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693

<210> 228<211> 439<212> DNA<213> Homo sapiens

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120gagacaagaa acgtgtatt ttccgtgcac ggacacggg caacttgtct tcctcagaaa  
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439

<210> 229<211> 778<212> DNA<213> Homo sapiens

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<210> 230<211> 440<212> DNA<213> Homo sapiens

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<210> 232<211> 536<212> DNA<213> Homo sapiens

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<210> 233<211> 721<212> DNA<213> Homo sapiens

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552

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665

<210> 236<211> 128<212> DNA<213> Homo sapiens

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128

<210> 237<211> 720<212> DNA<213> Homo sapiens

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720

<210> 238<211> 436<212> DNA<213> Homo sapiens

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436

<210> 239<211> 411<212> DNA<213> Homo sapiens

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180ccaccgcaac tgtctgtctc atatcacgaa cagcaaagcg acccaaaggt ggatagctctg  
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300tcggcccgga ccacgctaag ggcgaattcc agcacactgg cggccgttac tagtggtacc  
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411

<210> 240<211> 668<212> DNA<213> Homo sapiens

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120gatgtttcta tagtcacttt gccagctcaa aagaaaacaa taccctatgt agttgtggaa  
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668

<210> 241<211> 693<212> DNA<213> Homo sapiens

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120tgtttccctg ccccagaca ccataaatgc attgtaattt tgaaaatata tgccaactac  
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240acaagaaaat ctataccatc atgctacaga cgtacttaga aaacttaaaa ggaagagtaa  
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360atgaacatta tttgaacatt caacacatga aagggttaacc aaaggctatg aacttggtgt  
420aaacttaaac gttcanatgc gggagtcacc canatgtaat tgggatccag ggggatcccc  
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693

<210> 242<211> 488<212> DNA<213> Homo sapiens

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120agaacaaact gaaaatatct ggtatcagt ctctgaaatc ccaactatga aagccatata  
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488

<210> 243<211> 483<212> DNA<213> Homo sapiens

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180cctgctggga tcagtgaatg cctgattagg acatggggct atgcatagcc taagagttat  
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420actagtggat ccgagctcgg taccaagctt ggcgtaatca tggatcatagc tgttttccct  
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483

<210> 244<211> 385<212> DNA<213> Homo sapiens

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385

<210> 245<211> 545<212> DNA<213> Homo sapiens

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420caatagtcag ttctgcagac ctcgcccgcc gaccacgcta agggcgaatt ccagcacact  
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545

<210> 246<211> 312<212> DNA<213> Homo sapiens

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120tacagcagtt caagccgcgg agcaccaaga ggtgggtggcc gtggaggaag ccgatctgat  
180agagggggag gnagaagcng atactaaaaa caancaannc ttggaccaaa aatcccaggt  
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312

<210> 247<211> 569<212> DNA<213> Homo sapiens

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420cccttgagg gtatccgccc agttctacat naacctggaa ccaagaagag tnggaagctg  
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569

<210> 248<211> 287<212> DNA<213> Homo sapiens

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180acagctctgc cacacgggcc agcagtgtc atgtctgctg gctgacctc cccaaagcct  
240ctcctgccac cttttttttt tttttttnaa cnaanaaaaa gggaaaa  
287

<210> 249<211> 631<212> DNA<213> Homo sapiens

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 526

<210> 251<211> 539<212> DNA<213> Homo sapiens

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 420taattagctt tacctcggnc cgcgaccacg ctaagggcga attccagcac actggcggcc  
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<210> 252<211> 341<212> DNA<213> Homo sapiens

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 240cagtaacagt tacttttgag agttttcttg tcaagctttt accaggcatt ctctagcctt  
 300ggtacaaaaa aaaaaacctg ctggtngcgc aaatncctag g  
 341

<210> 253<211> 650<212> DNA<213> Homo sapiens

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650

&lt;210&gt; 254&lt;211&gt; 430&lt;212&gt; DNA&lt;213&gt; Homo sapiens

ctcaaagtga taaaccatta agtagtcaaa tggctacagt gaaaaacagt attttatagt  
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360ctgtnatgaa aatntttnc cngganangg atttnggatn gctacgaaga acggaattcg  
420gattccnctt  
430

&lt;210&gt; 255&lt;211&gt; 239&lt;212&gt; DNA&lt;213&gt; Homo sapiens

gtcgcagtag ttccagtagc agctccagta caagtggcag cagcagcaga gatagtagca  
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120atagaaagca cagaaggagc gtggatnggn agagaaggga tntncagga atggaaagat  
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239

&lt;210&gt; 256&lt;211&gt; 282&lt;212&gt; DNA&lt;213&gt; Homo sapiens

aatgactgt gctgcccctt tcacatcaaa gaactactga caacgaaggc cgcgcctgcc  
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180tggcccaagg tgtcctgcag gctgtaatgc agtttaatac gagtgccatt tttttttgt  
240ncaaagtatt ttaattattg gaatgcncaa ttgntttaat at  
282

&lt;210&gt; 257&lt;211&gt; 722&lt;212&gt; DNA&lt;213&gt; Homo sapiens

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540gcatgctctt tggcacttac atgaaagtga aaaatgaagg aaggagaagt gtaaaccttg  
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720cg  
722

&lt;210&gt; 258&lt;211&gt; 689&lt;212&gt; DNA&lt;213&gt; Homo sapiens

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360ttttgttaag tcttttacat tttaatagtt tttgaagaca atctaggtta agcaagagca  
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540agtactttca ggaagactga cttaaatatt tcgggggtgga gtaangagnt ngggnattaa  
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689

<210> 259<211> 701<212> DNA<213> Homo sapiens

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701

<210> 260<211> 577<212> DNA<213> Homo sapiens

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577

<210> 261<211> 177<212> DNA<213> Homo sapiens

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177

<210> 262<211> 333<212> DNA<213> Homo sapiens

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333

<210> 263<211> 518<212> DNA<213> Homo sapiens

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360agtacctana catctataac taacaccact tttcttacta tcattgaagt caatanaaac  
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518

<210> 264<211> 364<212> DNA<213> Homo sapiens

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120gagcaaacaa gagcaagaaa caaaaagaag ccaaaagcag aaggctccaa tatgaacaag  
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240agtgtgttaa gagtgataag taaaatgcac gtggagacaa gtgcatcccc agatctcagg  
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364

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248

<210> 266<211> 538<212> DNA<213> Homo sapiens  
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120aagcagtgtc taaaaattag atcggtccta aattggaatg ggatgtcttc cttgcatgtc  
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420catcntatca angaagttn tttntgant ttttccatct aaancctnt angtttgggt  
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538

<210> 267<211> 504<212> DNA<213> Homo sapiens  
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360gaaagctagt tctgatgcta aaattctgtt taagccaaaa aggtttacct gccggggcg  
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504

<210> 268<211> 220<212> DNA<213> Homo sapiens  
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220

<210> 269<211> 332<212> DNA<213> Homo sapiens  
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332

<210> 270<211> 421<212> DNA<213> Homo sapiens  
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<210> 271<211> 363<212> DNA<213> Homo sapiens  
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 120tacactttta ttttgggtatt tttgtcagtg caacttaaat ccttttactg acctgcagaa  
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 120gaagttggct tccatctcag agaagacgcc cagctttccc cgagagcag tgcacaccag  
 180gctcttgtgc aggtccagaa ggtcctgtc agccactagc accttgagct ccttcaagtc  
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 339

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445

<210> 276<211> 348<212> DNA<213> Homo sapiens  
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348

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399

<210> 278<211> 334<212> DNA<213> Homo sapiens  
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334

<210> 279<211> 376<212> DNA<213> Homo sapiens  
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376

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333

<210> 281<211> 347<212> DNA<213> Homo sapiens  
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180atggaaaaat gttaacaaat gtggcaatta ttttgatct atcaentgtc atcataactg  
240gcttctgctt gtcattccaca caacaccang acttaanaca aatgggactg atgtcatctt  
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347

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411

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291

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523

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379

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220

<210> 287<211> 431<212> DNA<213> Homo sapiens  
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420acttggcggg c

431.

&lt;210&gt; 288&lt;211&gt; 358&lt;212&gt; DNA&lt;213&gt; Homo sapiens

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358

&lt;210&gt; 289&lt;211&gt; 72&lt;212&gt; DNA&lt;213&gt; Homo sapiens

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72

&lt;210&gt; 290&lt;211&gt; 340&lt;212&gt; DNA&lt;213&gt; Homo sapiens

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340

&lt;210&gt; 291&lt;211&gt; 637&lt;212&gt; DNA&lt;213&gt; Homo sapiens

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540agaaaaaanc cttaaattga agggncctng gccggnaaac ccccnttaag ggcgaaattc  
600ccancnccct tggngggncg gttncntntg ggttccc  
637

&lt;210&gt; 292&lt;211&gt; 169&lt;212&gt; DNA&lt;213&gt; Homo sapiens

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120gaagaagtgg ggtggaagaa gtgggtggg ncgtctgngn tntcttgag  
169

&lt;210&gt; 293&lt;211&gt; 450&lt;212&gt; DNA&lt;213&gt; Homo sapiens

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120ggcacctgga aaacaaccca gctctggaga aactgctgcc tcatatccg gggaatgtgg  
180gctttgtgtt caccaaggag gacctcactg agatcaggga catgtngctg gccaaaggat  
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450

&lt;210&gt; 294&lt;211&gt; 337&lt;212&gt; DNA&lt;213&gt; Homo sapiens

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180gaaaagcttg atgggggtgc gggggaatct gggttggcctt aaagggaatt tggggncctg  
240ttcctgaatt tggtaggcaa gcatgcatgt aaggcttgaa gtgggtttgg acctgcccgg  
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337

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360gccttcctga cancttcntc atggcacttt tttaacnctt nancaaccaa acaccaaggc  
420nagacctcgg gcccgnaacc ccncttaan ggcgaaattc ccagcncact tggngggccc  
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542

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120caacaaggtc ggtagactct tcccagcata catctgagca tgtcaaaaatc tctccttcct  
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240gtattctgaa ctccattctc agctgggaaa gctacagatc ctttttagtgc aagataaggt  
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394

<210> 297<211> 493<212> DNA<213> Homo sapiens  
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240ttcccatcat aactgaggc tacagaactt ccttgagaa cagacccatt gttggcataa  
300actgtagtca ctgtaggct ctcagataga atgttctgga tgccgganaa cctctgaccn  
360aaggaagatt gttcnggtca tacacnaa ctttttgga ctgccgggcc gngcngtcaa  
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493

<210> 298<211> 390<212> DNA<213> Homo sapiens  
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120cttcaatcct aaagcagtga gacctcatt ttaacacaca gagcctccct gcctaccctc  
180cttccctgta acgtgagcta ctgtagtcca tttattagtt ctctggtaa gcttcagtag  
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390

<210> 299<211> 150<212> DNA<213> Homo sapiens  
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150



<210> 300<211> 399<212> DNA<213> Homo sapiens

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399

<210> 301<211> 654<212> DNA<213> Homo sapiens

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120aagcagtgtc taaaaattag atcgggtcta aattggaatg ggatgtcttc ctgcatgtc  
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240agattaaagg cttgagggat gaatttgatc atcattctta aagtcccttc caatcctgtg  
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654

<210> 302<211> 683<212> DNA<213> Homo sapiens

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240gggtggagagg gcacatctgg caaaagtctt cttgctagtg gggactctcc actttggcag  
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420atcatggaag ctcttaattt cctcttaaag gccctacctc tcaaaactgt catattgggg  
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683

<210> 303<211> 696<212> DNA<213> Homo sapiens

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120agagcagaga cagctcgtct gacttctttt attggtgcca tcgccattgg agacttggtta  
180aagagcacct tgggacccaa aggcattggc aaaattcttc taagcagtgg acgagatgcc  
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300gcagctaaaag ttttagttga tatgtcaagg gttcaagatg atgaagttgg tgatggcact  
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696

<210> 304<211> 531<212> DNA<213> Homo sapiens

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420cccgggcggn cgctcgaaag ggcgaattcc agcacactgg cggccgttac tagtggatcc  
480gagctcggtta ccaagcttgg cgtaatcatg ggcatactg gtttccctgg a  
531

<210> 305<211> 585<212> DNA<213> Homo sapiens

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480cctgcccggg cggtcgctca aagggcgaat tccagcacac tggcggccgt tactagtgga  
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585

<210> 306<211> 538<212> DNA<213> Homo sapiens

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120aacaccatan taatgtctaa tattcacagg cagatctgct tggggaagct agttatgtga  
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538

<210> 307<211> 590<212> DNA<213> Homo sapiens

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590

<210> 308<211> 440<212> DNA<213> Homo sapiens

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<210> 309<211> 688<212> DNA<213> Homo sapiens

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688

<210> 310<211> 213<212> DNA<213> Homo sapiens

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120attgtncaaa ggaggaatgt natatttaag gttcatttac aacgggcatt tggcgctgac  
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213

<210> 311<211> 730<212> DNA<213> Homo sapiens

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730

<210> 312<211> 690<212> DNA<213> Homo sapiens

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690

<210> 313<211> 698<212> DNA<213> Homo sapiens

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<210> 314<211> 691<212> DNA<213> Homo sapiens

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<210> 315<211> 699<212> DNA<213> Homo sapiens

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<210> 316<211> 691<212> DNA<213> Homo sapiens

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 691

<210> 317<211> 391<212> DNA<213> Homo sapiens

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391

<210> 318<211> 468<212> DNA<213> Homo sapiens  
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240aatgtggatg ggcttcgagc ctggattaag aagaaaggat tagattgggt aaaggaagaa  
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360ggccgcgacc acgctaaggc cgaattccag cacactggcg gccgttacta gtggatccga  
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468

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240agaatgcttt acatgattga gcaagtgcac gactgtgaaa tcattcatgg agacattaaa  
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420actatattca cagcaaagtg tgaaacatct ggttttcagt gtgttgagat gctcagcaac  
480aaaccatgga actaccagat cgattacttt ggggttgctg caacagtata ttgcatgctc  
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687

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240aaagcaagac agattaccaa agaagatttt gccacatttg attatatact atgtatggat  
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691

<210> 321<211> 385<212> DNA<213> Homo sapiens  
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180gactgactat atttatacaa cagaaacttt gtaatagatt ttttcagctt tgtgaaatcg  
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385

<210> 322<211> 642<212> DNA<213> Homo sapiens

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<210> 323<211> 712<212> DNA<213> Homo sapiens

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 600ttcttatcat cnccatcatg gcttacataa gtnagaataa atctgatggg caactgggan  
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<210> 324<211> 430<212> DNA<213> Homo sapiens

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 180gaatagagtt tgccccaaa tggaaaatta cacattattt tgtttcaaaa agttataaat  
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 300gtccgccagc aaatgagcat gctctgtcct ggaagccatt tttctttttc tttttttttt  
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 430

<210> 325<211> 693<212> DNA<213> Homo sapiens

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 540ttttcttggt tnagtgcntt gggacagatt tatattatgt caattgatca ggttaaaaat  
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<210> 326<211> 401<212> DNA<213> Homo sapiens

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 120ggaagactta tgaacgcctt gttgccagtt tcccagttc tggcagattc tggaaactgt

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<210> 327<211> 58<212> DNA<213> Homo sapiens  
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<210> 328<211> 479<212> DNA<213> Homo sapiens  
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 120tagaaaaatca aaagaggaat atgaccagga agaagaaaagg aagaggaaaa aacagttatc  
 180agaggctaaa acagaagagc ccacagtgc ttcagtgaa gctgcaataa tgaataattc  
 240ccaaggggat ggtgaacatt ttgcacaccc accctcagaa gttaaaatgc attttgctaa  
 300tcagtcaata gaacctttgg gaagaaaagt ggaaagggtc gaaacttctt ccctcccaca  
 360aaaaggacct cggccgcgac cagcctaagg gcgaattcca gcacactggc ggccgttact  
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 479

<210> 329<211> 635<212> DNA<213> Homo sapiens  
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 120acgctgttcc tcctttttcca tggagccaat ctgggtaatt ttttcattaa aattcttctt  
 180ctgcctgttt gctgcggaac tctttgagct gctgtagccg ctcgatagtt tcagaaatgg  
 240tgcgttcccc gtggacctta ttgtctcttg tgcggatatt aacagtgcc aatgatttct  
 300cttttttcacc aacaactaaa atgaagttat actgtgctaa ctgtgcattt cgaatctttt  
 360tattcaatgt acagcctgga tccagatcaa tgtctgccat gaatttggca tctgtgaatt  
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 480tggcgagggg acagccaaaa gggccatttg ccccatagt tttctgtgag gatagcaatc  
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<210> 330<211> 446<212> DNA<213> Homo sapiens  
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 60attaatttaa cagccttcca taagccatca ccattttgta agcataacag gcaagagagt  
 120caaagataac tgttagtggg aaaaggacaa cagttctaca tccatgcccc agaagccttg  
 180cccagtcagt ggtgacaact ccaggacagc ggcagaaaca cagtgaacct ttggagctta  
 240acaatagcca tgcaaaaaca catagattta tcttgcccc attctataaa gattggcttt  
 300gtagtatctt tccaagcatt tgaagagttt agtttggtag aacactgcta atttgaccag  
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 446

<210> 331<211> 290<212> DNA<213> Homo sapiens  
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 120gtcatttctt tttgggtaat gggaaagttc ttaagagtgt caatggggag gtagtagggg  
 180tgggggctna tggtttccct ctacttnggg agagggcaca gattgcagag gtaatgctgt  
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 290

<210> 332<211> 481<212> DNA<213> Homo sapiens  
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 60ctgaaagcca tccactatgc gttgaactgc tgtgggttgg ctgggggcgt ggaacagttt  
 120atctcagaca tctgccccaa gaaggacgta ctcgaaacct tcaccgtgaa gtcctgtcct

180gatgccatca aagaggtctt cgacaataaa ttccacatca tcggcgcagt gggcatcggc  
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 360agattggtgg gattttttgt ttgtttgtt ttgtttgtt gtngtttnt gntggttatt  
 420ttgccactaa ttttagtann cattctgctt tgctagataa aagctgaant gaccnaggtg  
 480t  
 481

<210> 333<211> 646<212> DNA<213> Homo sapiens

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 120ctggtctcag caagacatag gtactaattt ggttgaagca gataaccaag cagagtggac  
 180cgatgttcag aagaagatta tcccatggaa cagtcgtgtt tccgacttag acctggagct  
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 540aaangtttag acctaaccca atattgcntt cctganaaat tntntgctct tgnccgggaaa  
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 646

<210> 334<211> 423<212> DNA<213> Homo sapiens

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 240gacgatcctt tttccttcag cagcatttct tactggctgt ggctggaatc tgccttttat  
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 360tgatccnag ctcggtacca agcttgccg taatcatnng tcatagntga ttcctgggan  
 420acc  
 423

<210> 335<211> 528<212> DNA<213> Homo sapiens

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 180ctccagaaga aatgcctcag cttacaaaac atttatcaga aaacattaaa gataaattaa  
 240aagaaatggg atttgaccga tacaaaatgg tggtgcaagt agtgattgga gaacaaagag  
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<210> 336<211> 224<212> DNA<213> Homo sapiens

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 60ataataatta cattcatctt aatgtgtgtg tgccagttct gtttacatta acattggaaa  
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<210> 337<211> 393<212> DNA<213> Homo sapiens

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393

<210> 338<211> 483<212> DNA<213> Homo sapiens

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483

<210> 339<211> 618<212> DNA<213> Homo sapiens

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618

<210> 340<211> 495<212> DNA<213> Homo sapiens

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120ctgggtgaatg acccccagcc tgagcaccgc cttcgggctg acctagctga agaatactct  
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240cgacctgtgg actaaaatct gccacgattg gttccagcaa gtgtgagcag agaccccgctg  
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360ggcggttcgct tgtggagtac taacttttct acagtttttc tttattcnaa aaagnggcct  
420tnggggtaac cctggttnaa aagnaaaang ggatttttaa aaaaaatttt ttaaaggaaa  
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495

<210> 341<211> 88<212> DNA<213> Homo sapiens

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88

<210> 342<211> 610<212> DNA<213> Homo sapiens

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120cactctcctc caaaagagtt gatttctaaa tgaaaggaaa aagcaaacac aaataagaaa  
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610

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120gttannttaa catcatatat ttgnaatntt gaaacctgga  
160

<210> 344<211> 241<212> DNA<213> Homo sapiens  
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120ggcaaaactga cctgcccggg cggcgcgtaa gggcgaattc cagcacactg gcggccgtta  
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240a  
241

<210> 345<211> 364<212> DNA<213> Homo sapiens  
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<210> 349<211> 352<212> DNA<213> Homo sapiens

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482

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142

<210> 352<211> 438<212> DNA<213> Homo sapiens

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438

<210> 353<211> 644<212> DNA<213> Homo sapiens

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644

<210> 354<211> 343<212> DNA<213> Homo sapiens

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343

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387

<210> 356<211> 595<212> DNA<213> Homo sapiens

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603

<210> 358<211> 286<212> DNA<213> Homo sapiens

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286

<210> 359<211> 640<212> DNA<213> Homo sapiens

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<210> 360<211> 651<212> DNA<213> Homo sapiens

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<210> 361<211> 592<212> DNA<213> Homo sapiens

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<210> 362<211> 510<212> DNA<213> Homo sapiens

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571

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598

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<210> 367<211> 521<212> DNA<213> Homo sapiens

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<210> 370<211> 509<212> DNA<213> Homo sapiens  
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 300gaccacgcta agggcgaatt ccagcacact ggcggccgtt actagtggat ccgagctcgg  
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 240ctacaatgcc caagtcacac agattcttca gagccatcaa gtatttactt tctcccaagc  
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540ttccagcatg tattctatat tgcccaattg aatgtccatt tagattacgg gatnngntt  
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446

<210> 375<211> 448<212> DNA<213> Homo sapiens

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448

<210> 376<211> 680<212> DNA<213> Homo sapiens

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<210> 377<211> 648<212> DNA<213> Homo sapiens

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648

<210> 378<211> 670<212> DNA<213> Homo sapiens

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<210> 379<211> 566<212> DNA<213> Homo sapiens

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<210> 380<211> 612<212> DNA<213> Homo sapiens

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<210> 381<211> 607<212> DNA<213> Homo sapiens

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695

&lt;210&gt; 387&lt;211&gt; 590&lt;212&gt; DNA&lt;213&gt; Homo sapiens

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590

&lt;210&gt; 388&lt;211&gt; 403&lt;212&gt; DNA&lt;213&gt; Homo sapiens

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403

&lt;210&gt; 389&lt;211&gt; 466&lt;212&gt; DNA&lt;213&gt; Homo sapiens

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466

&lt;210&gt; 390&lt;211&gt; 386&lt;212&gt; DNA&lt;213&gt; Homo sapiens

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386

&lt;210&gt; 391&lt;211&gt; 721&lt;212&gt; DNA&lt;213&gt; Homo sapiens

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721

<210> 392<211> 200<212> DNA<213> Homo sapiens  
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178

<210> 394<211> 649<212> DNA<213> Homo sapiens  
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649

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131

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360gctacattat aatattctaa acaccagtt tacctcggcc gcaaccccgt taagggcgaa  
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503

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<210> 398<211> 259<212> DNA<213> Homo sapiens

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120gccatgtctc tantgatccn atnnaagcac attattgngc catttttcca cgtctttgag  
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259

<210> 399<211> 734<212> DNA<213> Homo sapiens

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120tgcccggtgc cgcctgctac tgagtaaggg gcattcctgt tacagaccaa ggagaactgg  
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420acctangacc anaancncc ccaagaattc agcgtcttg tttacttccc ccttgttcct  
480tgccagcaca aaaaccgggn gggcgntatt tgnctcntn aaaaaancc anccgtcccc  
540cnggnaaaaa attaacgnaa agaaggcttg ccanaaatat ngcttaaaac ntttttgga  
600cctcggccn nggaaccacn nnttaagggc gaaanttcca accncttg nngggcggt  
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734

<210> 400<211> 441<212> DNA<213> Homo sapiens

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120cctccccact gtccataaca cctocnacc ctacatctt tccatatac caacncttg  
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300angtttcctt ccnccccctn actnnnaatc ctacaggcng accctgact cncctggctt  
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441

<210> 401<211> 594<212> DNA<213> Homo sapiens

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120gctaagtatt gatactatt ccattcaca ttggtgttct ttttaagggt tgcaaatttc  
180agccaatttt gtactaaga ttgtctgat cagctcaaaa agatttggt tagtgtttc  
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594

<210> 402<211> 627<212> DNA<213> Homo sapiens

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600aattttattat tgcnggggatg aaaaaaa  
627

<210> 403<211> 100<212> DNA<213> Homo sapiens  
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<210> 404<211> 574<212> DNA<213> Homo sapiens  
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420ttacgtcctt gcccatgcag gtctccaaaa gagtggaaaa atncaagata aaaatggaaa  
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574

<210> 405<211> 719<212> DNA<213> Homo sapiens  
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719

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480gaacctgaa agncttttc antcctttg cgta  
514

<210> 407<211> 444<212> DNA<213> Homo sapiens  
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300aaatcaccag gtctaccaa tggctggn ctgcccggg cggccgttca aaaggcnaat  
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444

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435

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240cgtaatcatg gtcatactgt tttcctgtga  
270

<210> 410<211> 83<212> DNA<213> Homo sapiens  
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83

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120aatancanac gttattcccc anaccaaagg aaacatttca atatatggaa ttccttacag  
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660aaacaaagnc ttnaaccttt tnttttaacn ntttnggtt ttcctcccgg cgggc  
715

<210> 412<211> 573<212> DNA<213> Homo sapiens  
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573

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449

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550

<210> 415<211> 551<212> DNA<213> Homo sapiens

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551

<210> 416<211> 479<212> DNA<213> Homo sapiens

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479

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351

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120cttaccaaaag tcttgtangc ggcttatagt tcttttggct acaaatcat tttggaaata  
180aagatttttt actacaaaaa aaaaaaaaaa aaaaaaaaaa aaaa



224

&lt;210&gt; 419&lt;211&gt; 487&lt;212&gt; DNA&lt;213&gt; Homo sapiens

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480gggcata  
487

&lt;210&gt; 420&lt;211&gt; 543&lt;212&gt; DNA&lt;213&gt; Homo sapiens

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540aaa  
543

&lt;210&gt; 421&lt;211&gt; 347&lt;212&gt; DNA&lt;213&gt; Homo sapiens

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347

&lt;210&gt; 422&lt;211&gt; 545&lt;212&gt; DNA&lt;213&gt; Homo sapiens

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545

&lt;210&gt; 423&lt;211&gt; 544&lt;212&gt; DNA&lt;213&gt; Homo sapiens

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180ccaaaaacag tggataatth tgtggcctta gctacaggag agaaaggatt tggctacaaa  
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 536

<210> 448<211> 531<212> DNA<213> Homo sapiens

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 420tgtcgtacct tttgggcata ttcatacan gttggtccca ctggaactac cattacctgg  
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<210> 449<211> 500<212> DNA<213> Homo sapiens

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 120ctgtagccct ctttgttttg cctgatttct ctcttttgga atgggagtgt ttagccaatg  
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<210> 450<211> 433<212> DNA<213> Homo sapiens

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 120aaccctgaag tgcttgatat cacagaggaa actctgcatt ctgcttctc ggagggtgct  
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<210> 451<211> 434<212> DNA<213> Homo sapiens

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 120gcaacctgga atggctgaga caagaaagc tgtattttcc gtgcacggga cagggtcaac  
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 434

<210> 452<211> 477<212> DNA<213> Homo sapiens

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 360aagcatattt tatttacctt nggccgnaac ccccttaagg cnaattccan ccacttggng  
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 477

<210> 453<211> 535<212> DNA<213> Homo sapiens

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 120agaagctgtg cccagttcc acatttgatt acacatgtga gatttgctgc tgttgcaagta  
 180taaactag gtataatagg atttgaaatt gcattacagt tcataaaaaat tgaaaatgag  
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 420actgtaaatc ttataatttt acctgcccgg cggccgttcn anggcgaatt ccagacactg  
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 535

<210> 454<211> 560<212> DNA<213> Homo sapiens

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 120aaagtattat tagtacatag cagcttcata acagtttact tttttaatat aaagattttt  
 180caatttacac ttgtaggagt agaaaaaact aatatgctaa gtctgtaagc tacgcagcaa  
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 300tagctgagta aatgtaaacc atgtgcttat taactcttct atataaaata ttgaaccccc  
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<210> 455<211> 518<212> DNA<213> Homo sapiens

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 180tctgaaatag acatttagtg tatggaaata caagacagct aaagggctgt ttggttagca  
 240tctcatcttg cattctgac aattggcaag aaagggagat ttcaaaatta tatttcttga  
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 518

<210> 456<211> 609<212> DNA<213> Homo sapiens

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 120atgacaaata tggaaggaa gtcctattgt acttactaag cccagagat cctgcacata  
 180cagtacgaga aatcattgaa gttctgcaaa aaggagatgg aaatgcacac agtaagaaag  
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<210> 457<211> 339<212> DNA<213> Homo sapiens

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120ggcatggaca agatctatga aggccaagtg gaggtgactg gtgatgaata caatgtggaa  
180agcattgatg gtcagccagg tgccttcacc tgctatttgg atgcaggacc tcggccgcga  
240ccacgctaag ggcgaattcc agcacactgg cggccgttac tagtggatcc gagctcggta  
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339

<210> 458<211> 623<212> DNA<213> Homo sapiens

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120catgtggaaa ccaagctaga gataagaatt ctccctgat gcagttaggg gaaagggaaa  
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240ttcaagcaca gtacactctt tgcagggacg gccagatgtt cagagtggga gtggtacttt  
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480agaaaccacc agtnccttga tgaaccttca aanacttag ggggggaaag anaaaggaag  
540gatttcanan atnggggaca gaatggnggg aaaatgttgg gctnactggn aaggaaatgg  
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623

<210> 459<211> 438<212> DNA<213> Homo sapiens

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120tgcacgccct gagctacagc ctctcccaaa aggcattctc cccacagcct caacgccgag  
180caaggagcat caagggtttg tctcggttgt tttgttcttt ttacaaacta tagatatata  
240cagttgaaaa ctcaggattt ctagccaata accatagtta ccaccacctt acaataaaaa  
300agaaaatgcc agaaacatct ttacctgcc gggcgngcgc tcaaagggcg aattncaaca  
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438

<210> 460<211> 381<212> DNA<213> Homo sapiens

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120cccagatcct gctgaaggcc ctcaccaact tgccgcacac agacttcacc ctgtgcaagt  
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381

<210> 461<211> 625<212> DNA<213> Homo sapiens

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120tgtttctcat ctggccttaa aatccatgaa agctggaaaa tcacaaggca tctgtgcata  
180tactggtgga ttttaatgag agtctgtgt ttggagcacc agaaataaac cagcttcaga  
240agcaaaagtta acaggaggag gaagcagagc tagagatgga aggagacca gccagcccgg  
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360tttattttgt aactaacgaa tactggcaca tgatctgaac ctnttttgac actnttttt  
420naagcttgac ccagtgggaag aaccttanga anggagaaac tcncccantc ttgccnnggt  
480cacaanaatg atcattcttn aaaaattttc ctnggggagt naatgggnaa atttnncttg  
540ggctnttttt cccgattgaa gaaggaacct tnaagnaagg gtttggggac cccgaantnc  
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625

<210> 462<211> 518<212> DNA<213> Homo sapiens

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120cagtatgcta ttaagaagtt tgctgaggca tttgaagcta ttccccgcgc actggcagaa  
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360cagtcactgt acttaaaagt ggatcaaaat catcatggca aaaaccagaa cttgcccggc  
420nggccgttca aaagggcgaa ttccagcaca ctggcgggcg ttactantgg atcccaacct  
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518

<210> 463<211> 583<212> DNA<213> Homo sapiens

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120tcaaggccca ctcaaggcct caaattagcc aatgggtgaat atggatatag gacttttaga  
180gggatgcagg ttgagttgta cataacttag aggtgaagtg cagggtccgaa acagggctag  
240actttggaga actgtaaaat ggctcactga gcatgacagc atcaggaccc ctggagtggc  
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360tgaacactgc gcatcatggg aaggtgaaaa agaaaaaggg ctagttaaaa tcttgntttt  
420ctggggggcc aacttangag gagcctaaag ctaacccttg ggcttgacan tntactttta  
480ccttactaca ctgtgcaatg aatgccnang ccanataaac ctnggccnaa cacctanggg  
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583

<210> 464<211> 303<212> DNA<213> Homo sapiens

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120acagtggctg gcggtgcctg gacgtacaat accacttccg ctgtcacggg aaagtccggc  
180atcagaagac tgaaggagtt gaaagaccag tagacgtcc tctactcttt gagacatcac  
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303

<210> 465<211> 540<212> DNA<213> Homo sapiens

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120caacctacta ctaatcacag accacaaggg taatgaccaa atttatgtgg tttttgact  
180ccatagttgt cttagcccaa tctttctata ctcttacgat tacttgggtt aacgcttctg  
240tgaggacctt ctggnctctg agatacccta aatatttaag atatttanat atcttgaana  
300tagtatagga tatagagatt gtaccaaata ggaatataag gagtattgtt aaaatgacca  
360gatccccgtt gatngtttta cntgacctaa ccaaattgnt ggaaaaagga aatcaaaacc  
420ttggattttt cnggggttna tncctgggtg ncaannccga aangntccc gaaaaggcnt  
480tcccttggtt naaacnggga anntgaaaca aaaaactttg ggtntttaga atcacttttt  
540

<210> 466<211> 83<212> DNA<213> Homo sapiens

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83

<210> 467<211> 618<212> DNA<213> Homo sapiens

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120gctcgctgcc actacctgaa gggtaaactg aggcattctca agactcagat ccagaaattc  
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 540ggcatggatt ccggtggaagg aacaaccctt aaacccaaaa agggcaaaact ggccggggggg  
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 612

<210> 469<211> 454<212> DNA<213> Homo sapiens  
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 120agggagagta caagatcatg gttgctgccc tgggctgggc cactgctgag cttattatgt  
 180cccgtgcat tcccctatgg gtcggagccc ggggcattga gtttgactgg aagtacatcc  
 240agatgagcat agactccaac atcagtctgg tccattacat cgtcgcgtct gctcaggtct  
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 454

<210> 470<211> 452<212> DNA<213> Homo sapiens  
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 120tatggtgtgt taataacaat aagaaactta gggaagcagg ctgtggactt ctggaattac  
 180caacaggaat gaggaagaa gaaaactgga gtttccagtc tctgagttct acccgatgta  
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 360cgntcgaaag ggcgaattcc agccactgcg gccgttctag tggatccnan ctcggnccaa  
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 452

<210> 471<211> 451<212> DNA<213> Homo sapiens  
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 180tccaattcgt ttcagttaca tgaacgaact cacactggag agaaacccta tgaatgtaag  
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 420naagcaactt tgtntntnaa ggtnttaaat g  
 451

<210> 472<211> 602<212> DNA<213> Homo sapiens  
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 602

<210> 473<211> 480<212> DNA<213> Homo sapiens

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 180tggtggaaac acaggaacaa attctctaag agactgtgtt tctttagttag agaagaaact  
 240tcattgagta gctgtgatat gttcgatact aaggaaaaac taaacagatc acctttgaca  
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 360ttgaagatga ttcctaaaaat gctaaatgna aatatatttg cttcccaaan ggnntttatt  
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 480

<210> 474<211> 444<212> DNA<213> Homo sapiens

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 120aacggaaaaa ctgggaacct tgggtggagg gtggtgacca tcgaaaggag caagagcaag  
 180atcacctgta catccgaggt gcctttctcc aaaaggtatt tgaaatatct caccaaaaaa  
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 300taccgaatta cgttacttcc agattaacca ggacgaagaa gaggaggaaa gacgaggatt  
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<210> 475<211> 563<212> DNA<213> Homo sapiens

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 120tttcttctcatt ctgttcttgc gttcctttcg ttgctttctt gaggtctttt tcttctcata  
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 240ataaatcatg ccaaagccag ttgtcttgcc accacaaaaa tgagttctga atccaaatac  
 300aaagatgaca tccggtgtgg tcttgatcat tttggctagt ttttcccgaa tttctgtctt  
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 420cggttggtca tgaactttct agtgcggata gttaccgggg tcgacctcgg ccgcgaacac  
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<210> 476<211> 426<212> DNA<213> Homo sapiens

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 120atgcagaaac agcttaataa tttgactag attagacaaa cagttaatag atccaccatt  
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<210> 477<211> 410<212> DNA<213> Homo sapiens

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120gccagtttgc tgatggccgc caaagttgga gttcgtatgt tgatgacatc tgattagcag  
180aagtcattgt ccagcttggc ctcatgaagg attaaaaatc tgcattctcc actattttca  
240atgtatttaag agaaataagt gcagcatttt tgcattctgac atttttaccta aaaaaaaaaa  
300aaacnccaan ttngncggag ggggggaaaa tcantngtaa cctttttaac cntacanaag  
360nggggggagc ttntaanatn gaccttattg anacntctt aaaaaccatt  
410

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120tttcagaaga tggacacaaa gaagaaggag gaacagttga agcttctcaa ggagaaatat  
180ggcatcaaca cagatccacc aaaataaatg ttttctacat tttcatttgg actaaatccc  
240acgaatgaca actaccacct ttttttccct ttttaattaat actaaatatt gtgatttctt  
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385

<210> 479<211> 467<212> DNA<213> Homo sapiens  
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120cctttttgtt tgtgtctcct aaagcccagc ccatgcctg actttgggtc ccagtggagc  
180ttgtacattt gtggatatta aatctttggc aaagtcattt acctgggctg gaatagggtc  
240cttggctgat tctttttcct aaacaccac ccaatgggag aggctgatac tcaacatgca  
300aaccttggtt tttatttctc caggcgaagg gatgttgga gacattctgg aaggggtggg  
360gtgtgaagat ttacaaataa tctttgaata tctgcttnat gataggctt ggagngcct  
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120cacagaccag tggctccctg tccaaggccg cagagcagac gccatcccac tgtacaatag  
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420tgggtaaatg aatggtgctt aaaaataaaa tttattaata aagaagggga aaaaggagta  
480actctccctg actaaangta ctctaattaa ttatttctt ccaattaagn aaaccggaa  
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601

<210> 481<211> 392<212> DNA<213> Homo sapiens  
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392

<210> 482<211> 536<212> DNA<213> Homo sapiens  
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120caggctgcaa acatattacc acttgatgga ggcattcatgc tctggctgca atccgtgtgc  
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<210> 483<211> 150<212> DNA<213> Homo sapiens  
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 120ccgctcgtntt acaacgtcgt gtcactaat  
 150

<210> 484<211> 571<212> DNA<213> Homo sapiens  
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 120aataattacg caggtcagcc accactgcag aaccatcact gtcagagga attgagtcag  
 180caatgactga tctcatcatc tcttcattag cacataagcg gttcaacttg ggatacgcaa  
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 120aaccaaaaca tttctgggat atgtgactta aggaataaaa aaactcagtg ttttataaaa  
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 240aaataactta aaaatgtttt ataacaaaa atcaaatga aacaaaactt ggtagttgaa  
 300tataagtatt ttcaactgtt acaatacttg aggagatttt tgggtctaatt ttctcagaaa  
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 420natctaggat tacaanactt atnttttaca annacatcca tnntttctta aaatttantt  
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 509

<210> 486<211> 253<212> DNA<213> Homo sapiens  
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 120tagttaaaac tgcttttttag taaatttggt tttctttgca gatatgaggg aaggcaccat  
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 253

<210> 487<211> 569<212> DNA<213> Homo sapiens  
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 569

<210> 488<211> 694<212> DNA<213> Homo sapiens

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540ttttactaaa aaacncacaa tcagatacgg aagacctctt atctcacacc acaggccgcc  
600aatccngaana aagatatgga atntgaccna naggtgcaac aatgcttgaa aaaatggtga  
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694

<210> 489<211> 511<212> DNA<213> Homo sapiens

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360gccagcacag aacatgtccc tgtcagcaaa agtactgggt ggacctgcc gggcgggccc  
420tcaaaggcg aattccagca cactggcggc cgntctantg gatccaactc ggaccaagct  
480tgcngtaana tggcatagct tgttccgggg a  
511

<210> 490<211> 569<212> DNA<213> Homo sapiens

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569

<210> 491<211> 221<212> DNA<213> Homo sapiens

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120tccagacctg gaatccagaa cctcaaactc gtgagtggaa tgtcttgaga tgggcacgtg  
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221

<210> 492<211> 482<212> DNA<213> Homo sapiens

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482

<210> 493<211> 192<212> DNA<213> Homo sapiens

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192

<210> 494<211> 484<212> DNA<213> Homo sapiens

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420acnctgcng gcgtctangg atccactcgn ncaacttgcg aatatggcta ntgttcntag  
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484

<210> 495<211> 488<212> DNA<213> Homo sapiens

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488

<210> 496<211> 468<212> DNA<213> Homo sapiens

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240ggaccaccac ccctgggtga aagaaacaac actaaagaac cctaanaaca cccacacacc  
300ctgactccac cacctctggg catctgtggg cgtttgcttg tttgaacaga tccagtctca  
360ggaaaganga agacctgcct cggcccgacc cnctaaggcg atnccaacnc tgccggccgt  
420ctagtggatc gactcgtcca acttgcgtat atggcatgct gttctgtg  
468

<210> 497<211> 341<212> DNA<213> Homo sapiens

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120aacctcaaaa ccaaagagaa atctctgctt gcanagatac aaagaaagta actctccctc  
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240tatcaagan antcttcta cactggcgc gngagacngt nagaactctg aaatcacatn  
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341

<210> 498<211> 509<212> DNA<213> Homo sapiens

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180tagcagcatg ggggttccga gtgcatctga cctggagacg aaactgtaga gtatctatct  
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300gaatgagccc canacggtga gcaagaatct cattctgaca atggatgatn attgtcccag  
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<210> 500<211> 80<212> DNA<213> Homo sapiens  
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<210> 501<211> 23<212> DNA<213> Homo sapiens  
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<210> 502<211> 512<212> DNA<213> Homo sapiens  
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 300ttgatcatca ttcttaaagt cttcaatcc tgtgatnctc tgattccctg agtctcgta  
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 123

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<210> 516<211> 502<212> DNA<213> Homo sapiens

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515

<210> 519<211> 476<212> DNA<213> Homo sapiens

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476

<210> 520<211> 481<212> DNA<213> Homo sapiens

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480t  
481

<210> 521<211> 499<212> DNA<213> Homo sapiens

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499

&lt;210&gt; 522&lt;211&gt; 481&lt;212&gt; DNA&lt;213&gt; Homo sapiens

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480t  
481

&lt;210&gt; 523&lt;211&gt; 476&lt;212&gt; DNA&lt;213&gt; Homo sapiens

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476

&lt;210&gt; 524&lt;211&gt; 478&lt;212&gt; DNA&lt;213&gt; Homo sapiens

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478

&lt;210&gt; 525&lt;211&gt; 136&lt;212&gt; DNA&lt;213&gt; Homo sapiens

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136

&lt;210&gt; 526&lt;211&gt; 28&lt;212&gt; DNA&lt;213&gt; Homo sapiens

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28

&lt;210&gt; 527&lt;211&gt; 399&lt;212&gt; DNA&lt;213&gt; Homo sapiens

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399

&lt;210&gt; 528&lt;211&gt; 507&lt;212&gt; DNA&lt;213&gt; Homo sapiens

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 120tatgacctgt gaagacctca gcaacctgga atggttgaga caagaaacgc tgtattttcc  
 180gtgcacggga cacggtcaac ttgtcttctc cagaaagttc atccataccc aggatggcaa  
 240tgatatctct gagggatttg tagtcttgca agatcttttg caccacacgg gcaacatcgt  
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360cagactcggc cgcgacacgc taanggcaat tccagcacac tgcggccggt ctagtggatc  
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457

<210> 535<211> 77<212> DNA<213> Homo sapiens

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77

<210> 536<211> 430<212> DNA<213> Homo sapiens

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120agccccctcat gttgaggggg tgggttgac aatttgcaa cagattctaa ttctcttca  
180ccgtcagcac caaactggct gggaccacca ccctgggtg aaagaaaca cactaaagaa  
240ccctaaaaaac acccacacac cctgactacc accacctctg ggcattctgt ggcgtttgct  
300gttgaacaga tccagctcng aaagaagaag actgcctcgg ccgcaccnc taanggcgaa  
360ttcacacact ggcggncgtt ctatgatccg nctcgnccaa cttgcgnaat ctggctactg  
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430

<210> 537<211> 508<212> DNA<213> Homo sapiens

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120aaaatcattc ataatccac caccgagagg ctgtactttc ttcatcctt cacaagttat  
180gtccatatat gtaatatata aatgtctttt tacctttcaa aaatatgata ttacatatatt  
240acttagcctt ttccattttt atatcttacc aagaacctct tttttacaaa tgtgtaaagt  
300tctttttatta aaagacagag actttagat tggncanaat acaatnaaca atgagatgca  
360gatacaagag atcatctaaa ccattaatag cacnnggtat aagtngaatt ggccaaggat  
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508

<210> 538<211> 512<212> DNA<213> Homo sapiens

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120aaaataaaat agtaacctct gttcaatgt acagtttcca gaatctgcca gaactgggga  
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300caagtagtgt gattggaccc atagagaang aaatgtaatc tattactaa acctgtgcct  
360ctcgaatgag atgtcgaagc atcaaggcat atggatctct ctaattcttt ccgtttcttc  
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512

<210> 539<211> 46<212> DNA<213> Homo sapiens

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46

<210> 540<211> 172<212> DNA<213> Homo sapiens

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120ggtanatata tntcnaaata ncnnnacaat tgcnctaaat tctangatat ca  
172

<210> 541<211> 493<212> DNA<213> Homo sapiens

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120tagctaaaaa catagatgca aatgaaattc cccagagaa caaactgaaa atatctggta

180tcagtgtctct gaaatcccaa ctatgaaagc catatacaca aaaatgtaac ccttatatca  
 240ttgcaggaca atggaagaag gcagttcagt ggttgatcag tgtgctcaag caaataaaaat  
 300taaataaaaa ttaaaaatgg cagaatggta gctaaccctt gagaacangn taatgaaata  
 360tttgtctatn cttaaacatt aagtaaaaga agtgaatgaa ctcattactg ccgggcgggcc  
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 493

<210> 542<211> 470<212> DNA<213> Homo sapiens

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 120tgtgggtcgt ggataaggag cttattcagg ttctctgcc tagctattag ctccacttca  
 180catgctggag accggcgtag ggacagatgt attcatcctg gngttactga aaaacagggtg  
 240tgatcctggt actgatacta taagtgcact aaaatgcact gttcaaatta gccagngtct  
 300aacaaactaa actcttcaaa tgcttggaag gatctacaaa gcaatcttat agaatggggcc  
 360aaataaacta tgtgtttgca tggatattgta actccaangt cctgggttctg ccgtgtctgg  
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 470

<210> 543<211> 513<212> DNA<213> Homo sapiens

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 180tacaaaaaact gatttttccc ataaatattt ttacttcaga ggactaggac cattttgttt  
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 360ttcatctggc ctcacagcat gcgtgtgggn cttntgagc ccgaanaggt ttggnaagat  
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 513

<210> 544<211> 409<212> DNA<213> Homo sapiens

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 120gaaaatacag ccaggtccta gccaatggtc tggacaacaa gctccgtgaa gacctggagc  
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 240gccagcacac caagaccact ggccgcccgtg gccgcaccgt ggggtgtgtcc aagaagaaat  
 300aagtctgtag gacctcggcc gcgaccacgc taangggcaa ttccagcaca ctggcgggccg  
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<210> 545<211> 358<212> DNA<213> Homo sapiens

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 120gtccattaaa cctctttgtc ttcataaatt acccantctc gggatattct ttatttagcag  
 180cgtgagaaca gactaatata gtaaattggt aatggtatag agtgggggtg tgctataagg  
 240atacctcaaa atgnngaagc anattttgaa ctgggtaaca ggcaaaggct ggaacagttt  
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 358

<210> 546<211> 529<212> DNA<213> Homo sapiens

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 120atgggttgat gatattgtct ttggcggttt tcaagaaata tcaatcaaac cgtaattaaa  
 180tttcaacgta tcggctaaac atccactgag cacctcctct tgcagttagc attagactaa  
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420tgnaggccgg cggangncct gtcncctttg ccctgncaat ggccctcggcg naccctaggg  
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529

<210> 547<211> 393<212> DNA<213> Homo sapiens

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120acttaatact gccaacatgc ataacacatg ccagaaaagc tcatgcatta ttggaagaga  
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240tctttcttca gggataccat ttacctgcaa tgtgtaagaa tgaatatggg caggagttag  
300tcagggcatg gatactttta gattttgagc caagcaaatt attgcaagga gaaaagttcc  
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393

<210> 548<211> 484<212> DNA<213> Homo sapiens

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120cattcagcag ggactcgtga aacagcagga tgttgatcag atgttttggg aggttatgca  
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240tgctggggac catgcctgaa ctccccgaat aactgaaaaa tggctgaata tttttatggt  
300tacttgatat ttattttccaa ggagtgaacc taagactttt ttcccccttt gcaaatgtct  
360ctaagaaagn cccataattc ttttacttcc cgggcggccg ttcaagggcg aattccagca  
420cactggcggc cgttactagt ggatccaacc tcggtnccaa gcttgcgnaa tcatgggcat  
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484

<210> 549<211> 522<212> DNA<213> Homo sapiens

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60tgattatttta catttttagta attggacaat cccggctcag gaggaggttg caagaatctg  
120caaaagtttg agggagcgcc ccaggagaac aaacagcaag ccttatttcc cctagcccat  
180cccccaaaaa accatccatc ccctcctagt gtctggtggt gtccggtggt gtccatcttc  
240cattccttcc caaattatgg aagtaagggt ctctcacca gaataagagc acttgggata  
300acagagtang gtccccctcac ccaaaaaaaaa aaaaaaaaaan ctttggggga anaaaaangg  
360gttttcttcc ccccnaaaaa aaaaaaaaaatn ggggtttggg ggggggaaan ccnntttccc  
420cccatttttg gccccctngn tttnggggaa anggggcccc ttttccaaaa aaaaaaaaaac  
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522

<210> 550<211> 531<212> DNA<213> Homo sapiens

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120gcctatttct cggaacagca cttagtagtc ttcttaaagt tatattcaaa gttgaaactg  
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420tgggccaaca gacctgctcg ggcggccgtt cnaaaggcg aattccagcc cactggcggc  
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531

<210> 551<211> 572<212> DNA<213> Homo sapiens

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420ccanaacctg nccccgggccg ggccgnttca aaggggcgaa atttccagcc cacttgggcc  
480ggcccgttta cttangnggg aatncccaan ctttgggtna cccaancctt tgggccgtna  
540attcattggg ncattaanct tggtttcccc tt  
572

<210> 552<211> 419<212> DNA<213> Homo sapiens

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240gtgctggaaa cctcttttcc atcttggaat tgcctctgcc cacatntggg aagtgccata  
300nccttgagtg aattnatttg tntatntatn aaatcttttt cttctctcag gatacatcat  
360tcactttttg gggacctnaa agaancnat taactgatna atttgtgaaa ctaanaant  
419

<210> 553<211> 575<212> DNA<213> Homo sapiens

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575

<210> 554<211> 241<212> DNA<213> Homo sapiens

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120cttaccaaag tcttgttagg tggtttatag ttcttttggc taacaaatca ttttggaaat  
180aaagattttt tactacaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa  
240a  
241

<210> 555<211> 428<212> DNA<213> Homo sapiens

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120aaacaagact ggggctgctc ccattcattga tgtggtgcga tggggtactt acaaagtctt  
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300ggaggaggatt tcattaaatg cttactactt ttaccttggc cgngaacccc cttanggcgn  
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428

<210> 556<211> 666<212> DNA<213> Homo sapiens

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120tctgttttcaa ctttaagatt ctattaattt attcttacia caaataacca gtgggtttat  
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600acnttggggg ggccggttnc cttagtgggg aatccccnaa ctttngggnn ccccaaant  
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<210> 557<211> 360<212> DNA<213> Homo sapiens

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<210> 558<211> 53<212> DNA<213> Homo sapiens

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<210> 559<211> 564<212> DNA<213> Homo sapiens

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 564

<210> 560<211> 536<212> DNA<213> Homo sapiens

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 480cccctaangg cnaaattcca acacacttgg cnggccgntn cttagnggga atccca  
 536

<210> 561<211> 778<212> DNA<213> Homo sapiens

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 120aaataggcta aaatgaaaaa gaaaccgttg taacaagggt actaatcccc caactttcaa  
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600aangggggga nttgggcctt tttgtngcca aatngaacag ggTTTTTcc acatggtggg  
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745

<210> 563<211> 459<212> DNA<213> Homo sapiens

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180actctccaag aaactggaac tgctcctat tttggtttat gcagactgtg tcttggcaaa  
240ctggaagaaa aaggatccta ataagccct gacttatgag aacatggacg ttttgttctc  
300atttctgtat ggagactgca gtaaaggatt ctctctggtc tctctattgg tggaaatagc  
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459

<210> 564<211> 589<212> DNA<213> Homo sapiens

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120cttttcaagt tctgaactgg gaggtgactt tgagttcatg gatgatgcca acatgtgcat  
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360gnaactggct tcctaatttt cctacaaaag aatnatgtca ttgtaagnga atcctacctt  
420ggttggggcc cctaattaat ncttctngn taattaacat taatctttga cttttaaagg  
480ggttaacttg gaataagcct tggggttttn ggaaactgct tccccgaaan ccattcnaat  
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589

<210> 565<211> 103<212> DNA<213> Homo sapiens

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103

<210> 566<211> 502<212> DNA<213> Homo sapiens

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120atgagaagtt tatgggcct ccccaattg tctttttatt ttgggttatg acgatcatgt  
180ttgataatta caatgatagt ctctttccac gtgatgcttt tgtttgaacc tgataaaatt  
240tagtgaaact ttgtaatgat ctatgtgcac ttttacttgt aaaatggaat ttctgtatgt  
300ttatacttgt aaatatgatt gttgttagtg ctctgttgc tcatggtgtc ctgcctcgca  
360tttgggtgaat ctnnttaatg ancangtatt cttaactnat ttcntaantg gngtnggna  
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502

<210> 567<211> 358<212> DNA<213> Homo sapiens

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240cccagacctg cccgggcggc cgctcaagg cgaattccag cacactggcg gccgttacta  
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358

<210> 568<211> 438<212> DNA<213> Homo sapiens

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180agagggggag gcagaagcag atactagaaa caaacaaaac tttggacca aatccagtt  
240caaagaaaca aaaaaaagag tggaaactat tctatcataa ctaccaagg actactaaaa  
300ggaaaaattg tgttaccttt ttacctgcc cggggcgggc cgctnnaggg cgaatttcag  
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438

<210> 569<211> 609<212> DNA<213> Homo sapiens

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120aagatgggtga tggaactata acaacaaagg aattgggaac tgtaatgaga tctcttgggc  
180agaatccac agaagcagag ttacaggaca tgattaatga agtagatgct gatggtaatg  
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300gtgaagaaga aattagagaa gcattccctg tgtttgataa aggatggcaa tggntathtt  
360antgcttnaa aactnnccct tgtgatnaca aaccttggan anaagttacc anatgaanaa  
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480tcaaatagata cagcaaatga aaccttttca naatgtgtta aattcttnc aaattnttta  
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609

<210> 570<211> 544<212> DNA<213> Homo sapiens

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120ttctagggaa atggctttca tggagaaaag gaaaagagga agtgtagtat cagtctatgt  
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240atattttagaa aacaaattaa gtgaagcttc tggaggtagg gctgaaaatg gtgaaagaag  
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420cccttgnttt tactacaaaa aaaaaaaacn accttgaaaa attaanntan ntccacccca  
480agttnaaatn gcctccatta atttctttcc ccctnnaatc accnggatnt ttatttccta  
540tgct  
544

<210> 571<211> 279<212> DNA<213> Homo sapiens

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60ttgttggatt gttatttttt gtttgcaatg gggaatttat aagaagcatc aagtctcttt  
120cttaccaaaag tcttgttagg tgggttatag ttcttttggc taacaaatca ttttggaat  
180aaagattttt tactacaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa  
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279

<210> 572<211> 555<212> DNA<213> Homo sapiens

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120tgtaaaaaaa ggagagaagg atattcctgg actgactgat actacagtgc ctgcgccct  
180gggccccaaa agagctagca gaatccgcaa acttttcaat ctctctaaag aagatgatgt

240ccgccagtat gttgtaagaa agcccttaaa taaagaaggt aagaaaccta ggaccaaagc  
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420ttttggacct tngggccgcn aaccaccctt aangggcnaa attnccancn cacttgggng  
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555

<210> 573<211> 678<212> DNA<213> Homo sapiens

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120aagaggggaga gagaggaaaa gagagagaaa gagagagagc ggcgcgatgg ctgaaatcct  
180aggcgagaaag aaagattctt ctgcctgata gttattttta tgctctaaaa atcctgcaaa  
240tcagaccttc ctgtcccttg caggataact gtaaggcttt ttaatgtaag gaggcttctg  
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540tccccgnntt gccaaaaaac ttgatttnaa atagtcccct tggggaaaag catttcctt  
600anctcctgac ttnaatgccc tanttggccc ccttgggcgg aaccctttag gnaattcncc  
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678

<210> 574<211> 345<212> DNA<213> Homo sapiens

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120gatgcccac caccattattg aggggtggatc ttctgtactc agtctaccag tagaaatgtc  
180aatgacttcc agaaacaccc tcaccaacac acgtggaaat aatgttttac caggatatctg  
240ggcatccctt ggttcaactca agttgacaca aaattaacca tcacagaagg agactggcct  
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345

<210> 575<211> 514<212> DNA<213> Homo sapiens

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120aaaaggatta cttctccgag gagatagaaa tgtcaacctt gttttgctgt gtcagagaa  
180accttcaaaag acattattaa gccgtattgc agaaaaccta cccaaacagc ttgctgttat  
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360aaaacntga ggaagggana tntaaccctt nggtnttggg gaaagaccn ccggaccttn  
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514

<210> 576<211> 590<212> DNA<213> Homo sapiens

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120tcaagatcag taaatttaga aaaagcttca gagtctttga aaggaaacat ggctgctttt  
180ctaagaatg tgtgtctggg gttggaagat ctgcagtatg ttttcatgat ttcttcacat  
240gagcttttca ttacattgtt gaaagatgaa gaacgaaagc tacttggtga tcagatgagg  
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420ggaggattag accaaattta attgaatata tgggntgact ttanaacccc cntctggacc  
480gggnttaata annngggaaat nccttttttgn ttttnggggg ntancnggg aattaaana  
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590

<210> 577<211> 552<212> DNA<213> Homo sapiens

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120tattgataca aaggagaggt gttcagatca tcttgtaag atgcagagct caaaataaac  
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240tatgcagtat aaagcccaag tagaggggtg atttttaatg actactttgc ttacatttta  
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420agaaatgctt atctaccgcn ttntgangga gaaaacaana ncagnggcnt gnaaaatttt  
480ccaacnnana atcgtaatng ggttcaaag anccngtaa aaccattttt tnccttagg  
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552

<210> 578<211> 600<212> DNA<213> Homo sapiens

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240aaagtcaggg catcgaaagg cttcatccta tgcagtttga tcacaagaaa gaactgagaa  
300aacttaatat gtctatcctt attaatctt tggaccttt agatatttta ataangancc  
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420tntcttctnt tntaaatgaa ttcccgaccc caccaagcaa gaaaaaaacc ttganantca  
480tgattggang gnccaaaaac ctncaacggg tttgaaacag aacttngggc cgnaccacc  
540cttaagggcn aaattccaca ccctgggng gncnttactt ngnggggatc cnaactttgg  
600

<210> 579<211> 563<212> DNA<213> Homo sapiens

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120agtagttgga atgggaaggg agagtttgac ccgagacaga gcatgagctc ctcccaggaa  
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240gggtcaggag aaagaaagat catcaaagaa gaaagtcaac caaaaactgg aaaagagcgg  
300acccatccca ttgtttccac tgaattcatg tcatgagaac aagacttctn ggggccatt  
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420aacagttttg gacagtcaag ggcncaggc tatcaaacct cggccgagac ccccttaagg  
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540ttgggcgtaa tcatnggcaa tag  
563

<210> 580<211> 337<212> DNA<213> Homo sapiens

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60ttagatctta ttcacagcc tgctgaacag ttcctttttc agagacatag ataccatcca  
120aaaatttcct gatatacctt tttttaactg ttgtggcttg ctgaatcaaa gccgctgaat  
180ttgaaacaag ctcaatgtca tttccttcaa ggattaattc atctttctgg gcttgagata  
240ctgaacaagc aacacctggc tcatccgaa ccctgcggat atatttttca ccaagaaat  
300ttcggatttn aacaagagac ccattctnct ggataac  
337

<210> 581<211> 390<212> DNA<213> Homo sapiens

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120gacttggggg ttcaatattt tatatagaag agttaataag cacatggttt acatttactc  
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240tatttttgcg gcgtagctta cagacttagc atattagttt tttctactcc tacaagtga  
300aattgaaaaa tctttatatt aaaaaagtaa actgttatga agctgctatg tctaataatc  
360tttgctttcc aaagggttgg ggtttggtgg  
390

<210> 582<211> 380<212> DNA<213> Homo sapiens

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 180ttgataatta caatgatagt ctctttccac gtgatgcttt tgtttgaacc tgataaaatt  
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 380

<210> 583<211> 498<212> DNA<213> Homo sapiens

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<210> 584<211> 313<212> DNA<213> Homo sapiens

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 180tttactaagt attatgtgtg gttattatag attttcacaa agatatattg ctggtaatat  
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 313

<210> 585<211> 435<212> DNA<213> Homo sapiens

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<210> 586<211> 94<212> DNA<213> Homo sapiens

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 94

<210> 587<211> 586<212> DNA<213> Homo sapiens

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 586



<210> 588<211> 456<212> DNA<213> Homo sapiens

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456

<210> 589<211> 164<212> DNA<213> Homo sapiens

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120tttttttttt tttttttttt ttttttcccc cccccnggg gggg  
164

<210> 590<211> 256<212> DNA<213> Homo sapiens

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120cgtagccgtc cagagactgg caggacctcg gccgcgacca cgctaagggc gaattccagc  
180acactggcgg ccgttactag tggatccgag ctcggtacca agcttggcgt aatcatggtc  
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256

<210> 591<211> 592<212> DNA<213> Homo sapiens

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180cagaaccgga aggatctgaa gcctgggtcac canccggact gaagaattga accgggaggt  
240cgcttgagcc tcggccgcga ccacgcttaa gggcgaaatt ccancacact tggccggnc  
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374

<210> 593<211> 370<212> DNA<213> Homo sapiens

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180catccaaggg tgagaaacag cagagcctaa gtgagagtct gagtcaacac cttgggtcag  
240ttttcaaagt aattttacct gccggggcgg ccgctcgaag ggcgaaattcc agcacactgg  
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370

<210> 594<211> 591<212> DNA<213> Homo sapiens

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120tctagctgtc tgcgagcctg gctgtggtgc acatggaacc tgccatgaac ccaacaaatg  
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240acatgccctg aggccagcag gcgcccagct caggcagcac acgccttcac ttaaaaaggc  
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420aatgggtcatt acacttaana atctggnctg aattttntan ctctttataa aatacttgac  
480cgatattacc tcntcctttt aagtttctna atccttctgt ncctgaaggg ntanaatttt  
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591

<210> 595<211> 650<212> DNA<213> Homo sapiens

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120tattgtgcaa aggaggaatg taatatTTaa ggTtcattta caacgggcat ttggcgctga  
180cagaaaaagt ctttctatgt atacattcaa ctttttgag catatttaca ttcaagttac  
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360cctactaagt caactgcatt tttactactt taacaaaatt cactgacatt tttatccccg  
420ttgaagtcna acctcttttn naccaaantc aatacttact caatgggtgcc ngntttaaaa  
480tatatnataa tctcttttct cctctctttt aaaaaccgnn tttcaacntt caatgaaang  
540gccccccctt ttganaaatt tttttntttt tccagaaatt nggatggttt acaaanacca  
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<210> 596<211> 26<212> DNA<213> Homo sapiens

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26

<210> 597<211> 482<212> DNA<213> Homo sapiens

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180aagctgtgta ctgaatattg gtgcttgtaa actgaagatg tcaaattggc agggagcaat  
240tgacagttgt ttagaggctc ttgaaataga cccatcaaat accaaagcat tgtaccgcga  
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360ctcaggggat agcaccaga agataaacta tccaggcaga attgcttgaa agtcaaacaa  
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480at  
482

<210> 598<211> 562<212> DNA<213> Homo sapiens

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120caggaagtgc atagtctcaa aggcactttg tttctcccaa gtaggccacc aggcagctc  
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240acctgcccc tccacttccc tcagatgatg aggagccagg gctaagggg cagccttctc  
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420aaacccaaac ccanttgctc cccatgcnaa aagaaatcct gtgtgancct nttggtntta  
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<210> 599<211> 67<212> DNA<213> Homo sapiens

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67

<210> 600<211> 323<212> DNA<213> Homo sapiens  
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120cagtaagcca tgtgggaagt gctactttta cttcttgatt agtaagacat ttgtggaagc  
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323

<210> 601<211> 391<212> DNA<213> Homo sapiens  
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120aaaatgacaa agaggcagca ggagagggcc cagccctgta tgaggacccc ccanatcaga  
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240ttcgagcctg gattaagaag aaaggattag attgggtaaa ggaagaagcc ccaaatatac  
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391

<210> 602<211> 574<212> DNA<213> Homo sapiens  
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120ggagaaagaa agagaaaatc agttcgtggg tgcattgtgg atgcaaactc gagcattctc  
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574

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360caaataattat aggcagaaat gctaaagggt ttacctgcc nggcgggnccc tcgaaagggc  
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505

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120ggacattaat gggaaaaactg gtgagctaca ttatacaaaa taactgatca gtgctcttca  
180aggtgtcaag attatcaaag acataaaaaga atggatgaac tgccatagat tggaggagac  
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607

<210> 605<211> 555<212> DNA<213> Homo sapiens

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120caaagatggg cttggcgcct tttcctaggt ttccggtagg acggatgcca ttcagaactt  
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555

<210> 606<211> 450<212> DNA<213> Homo sapiens

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420cttggcgtaa tcatggcata ctgttctctg  
450

<210> 607<211> 379<212> DNA<213> Homo sapiens

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120cccagatcct gctgaaggcc ctcaccaact tgccgcacac agacttcacc ctgtgcaagt  
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379

<210> 608<211> 461<212> DNA<213> Homo sapiens

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360ggaaccaccc aacgtgatgc cttcaaagga agcacataaa agncttttta actgatgtca  
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461

<210> 609<211> 489<212> DNA<213> Homo sapiens

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489

<210> 610<211> 582<212> DNA<213> Homo sapiens  
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480cccccttctt aantttccct ggttgaaaac tttttgctgg ctgcccct ntngggaaac  
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582

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550

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510

<210> 613<211> 512<212> DNA<213> Homo sapiens  
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512

<210> 614<211> 437<212> DNA<213> Homo sapiens  
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437

<210> 615<211> 383<212> DNA<213> Homo sapiens  
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383

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455

<210> 617<211> 402<212> DNA<213> Homo sapiens  
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402

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597

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663

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115

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<210> 635<211> 479<212> DNA<213> Homo sapiens

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479

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479

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546

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338

<210> 643<211> 545<212> DNA<213> Homo sapiens

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337

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364

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240tttaaatgaaa cctgtntttg canaantgct tttnaaaaaa necttttttt ttctcttttt  
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361

<210> 649<211> 775<212> DNA<213> Homo sapiens

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660aaaaaaaang gggtncccn aaaaaaacc ttttttttt nttnaaacca aaataaaaaa  
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775

<210> 650<211> 343<212> DNA<213> Homo sapiens

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343

<210> 651<211> 275<212> DNA<213> Homo sapiens

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120cctcccccta ccctgagaga gctatcctgc ccataaacta tcaaagggtta gttttaggac  
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275

<210> 652<211> 470<212> DNA<213> Homo sapiens

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120aaggagctga ccagataaaa aaaaaaagt gattctctcc tggaaaacct ggaaaaaatt  
180gaaaaggaac agagcaaaac agcagtagag atgaagaatg ataagtcaga agaggagcag  
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<210> 653<211> 320<212> DNA<213> Homo sapiens

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320

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120ctgcttgctt ctctgttca acctgcccgg gcggccgctc gaaagggcga attccagcac  
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253

<210> 655<211> 541<212> DNA<213> Homo sapiens  
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420caaaggaang gcaggcgtga tggcttattt gntttgnatt cnaangattg cttttccctt  
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541

<210> 656<211> 442<212> DNA<213> Homo sapiens  
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525

<210> 658<211> 457<212> DNA<213> Homo sapiens  
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457

<210> 659<211> 596<212> DNA<213> Homo sapiens

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596

<210> 660<211> 332<212> DNA<213> Homo sapiens

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120tcgagtcgtg gtgcgtccag agagacaaat accgatactt tgcttgtttg atgagagccc  
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332

<210> 661<211> 274<212> DNA<213> Homo sapiens

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120gtcaggcctg gcctcatctc agacctgtg taggatgggg gatgtggacc tcggccgcga  
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274

<210> 662<211> 440<212> DNA<213> Homo sapiens

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440

<210> 663<211> 605<212> DNA<213> Homo sapiens

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<210> 664<211> 577<212> DNA<213> Homo sapiens

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577

<210> 665<211> 330<212> DNA<213> Homo sapiens

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330

<210> 666<211> 406<212> DNA<213> Homo sapiens

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406

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226

<210> 668<211> 397<212> DNA<213> Homo sapiens

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<210> 669<211> 451<212> DNA<213> Homo sapiens

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<210> 670<211> 36<212> DNA<213> Homo sapiens

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36

<210> 671<211> 102<212> DNA<213> Homo sapiens

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102

<210> 672<211> 488<212> DNA<213> Homo sapiens

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400

<210> 674<211> 424<212> DNA<213> Homo sapiens

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424

<210> 675<211> 496<212> DNA<213> Homo sapiens

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496

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459

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625

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240ctttaataaaa cactaaacta atagatcata gaaaactaaa agcttagaga aggtgcctcc  
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360atgctttttt ccaaggctgg gtccatgcct catttgtcaa attaacccca ttgaggaga  
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480ttgnaaaacn tttttaaaat aatttaaaac ccaagggttc ccnggtaaag ncccaacct  
540nttaaaaaaa aggggaaaac ctttgttctt ttaactttt aacattttt tccctacct  
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693

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120ttctgtctcg gtaactttt ctctctgcat ataaaatttc atgactaaaa taactttaaa  
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300gatgtgtgta ggaagatttt aaaattcagg caaattggtc tctaaagaga ccaattttgc  
360ttcctttgtc ttggttccaa taaggattta ntacaaaaa gttcaaaagg ctggcttncc  
420anaanaattg tacatacttc tctgaacccc caaaancaa ggaaaaaata cctctaant  
480tattatttat ctacggggtg aaaactaact accttatatt taaataaaca nccctaaatt  
540aatttattta attttgngg gggggcttna ggaancaatt tnagggggga aaaaaagg  
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638

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120aaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaanant aaaa  
164

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120gtacatcatg ttactgcact gaatactgta ggcaactgta acataatggt atttgtatct  
 180aaacatagaa aaggtatagt aaaaatacag tattacaatc ttatgagact gccaacatat  
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 300aacaaccccc tgtatccata gtgtttacct gcccgggcgg cgcctaaggg gcgaattcca  
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 120tctgctttca ctttaagtgtc tggcccgcaa tactgttaga acaagcatga tcttgttact  
 180gtgatatttt acctcgcccg cgaccacgct aagggcgaat tccagcacac tggcgncggt  
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 295

<210> 683<211> 440<212> DNA<213> Homo sapiens

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 120gggtagtctc ctttctggac tgagaagaga agaattggaga agccctctt cccattagt  
 180cctttgcatt ggtttggctt tggctacaca gactgggtt tttctgggtg gatcggtggc  
 240tatgtaaaaa caggaatcta gaaaactgta tctgaagtcg ttcctacctg aagcggttgc  
 300attgagaggt gctaagtggg tctctggcc agacctgcc gggcgccgc tcgaaagggc  
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<210> 684<211> 100<212> DNA<213> Homo sapiens

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100

<210> 685<211> 426<212> DNA<213> Homo sapiens

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 180atattctttg gntcttcag cctanacaca actcctgacc taanacattg agtggagagt  
 240cctaaccctt tggaagtga actttctgct ttcttcctgg gactttggaa ctgagtttga  
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<210> 686<211> 356<212> DNA<213> Homo sapiens

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 356

<210> 687<211> 259<212> DNA<213> Homo sapiens

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 120gatttttata agttttgtgt agatttttat gtttcatatt ttacctggc cgcgaccag  
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<210> 688<211> 543<212> DNA<213> Homo sapiens

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 360ggggccaatg gtcccaaaa aattcctggt cancncccc catttccaaa ggggccaatt  
 420ttcaaggaan ggcaggcctn aaggcttatt tggtttgna ttcaangatg gctttacca  
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 543

<210> 689<211> 417<212> DNA<213> Homo sapiens

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 180aaaatgtttc tctcatttac tctttaaaca aaagacttaa attagtttgg gtcattatnc  
 240tttattttgca gcatttggtt tgtattagcg taagagcaag tataggatat ggagaggccc  
 300tgctcatgaa acaaaggagg cccagggtata atacagtttc tctnccctct tactttntc  
 360ccanttttcc ctgtngttcc tttcccaatt gtnnattcct nctggccccc aaggga  
 417

<210> 690<211> 565<212> DNA<213> Homo sapiens

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 120gctctgacaa tggcaggaaa agaaaactca caggtaacta aacatttatc tagtaaggca  
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 565

<210> 691<211> 331<212> DNA<213> Homo sapiens

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 120agggagcttg gcttctgtag aagttctaag gaagcgttac gaactccacg gcggtggggc  
 180gctaactagc agggaccctt gcaagtgttg gtcgggggcc tcgagctgcc tgagctgaca  
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<210> 692<211> 333<212> DNA<213> Homo sapiens

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 120atatggtaac atgatcgtga ccttcaaaaca gcataaatat gtgtgcentc tcatgtgcaa  
 180ttccttatan acccagctng gttcttctcc aatgtctcct tttggagttg tacctgattt  
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 333

<210> 693<211> 326<212> DNA<213> Homo sapiens

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 180gggtcctagac caggccattg tttctggtaa tgtcccatct agcccagaag aagtggaggc  
 240tgtgtggacc tgcccggccg naangggcaa attccaccn ccttggccgc cgttactagt  
 300ggatccgagc tcggtacca gcttgg  
 326

<210> 694<211> 371<212> DNA<213> Homo sapiens  
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 120tccaaagaca aaacagaaca attattataa caaaataatt atgggtgaaa tgtctgtggg  
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<210> 695<211> 370<212> DNA<213> Homo sapiens  
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 180cttgctaact gttgtgattt taaagaacta ttgcagaagt ctgaagaaaa tagatttatt  
 240agtttaactta taaagagatt aaagaggntg aacaggtttt aaaagaaaat tggggctttt  
 300ttaaaaaggt anggttttaa atttccatt ttgaaaaaat aatggtggtg gtttggtttt  
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 370

<210> 696<211> 480<212> DNA<213> Homo sapiens  
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 480

<210> 697<211> 405<212> DNA<213> Homo sapiens  
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 120tgtgtgtaca tagttgactg acaaaattct ctaccatcca gcacccta taattgacga  
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 405

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600ggaatttttc tcttggaaaa aaantggggg tttttttt  
638

<210> 699<211> 443<212> DNA<213> Homo sapiens  
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443

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120gaaattactt taaaattata cacgtttgga acaacagatt ttttaaaaaa tgaagtttgg  
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353

<210> 702<211> 263<212> DNA<213> Homo sapiens  
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263

<210> 703<211> 100<212> DNA<213> Homo sapiens  
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100

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180acacgtacta aaggttgaac tcaaagatat gtacaggggt attaaacaaa taccaagggg  
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435

<210> 705<211> 601<212> DNA<213> Homo sapiens

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600t  
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<210> 706<211> 320<212> DNA<213> Homo sapiens

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320

<210> 707<211> 296<212> DNA<213> Homo sapiens

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296

<210> 708<211> 552<212> DNA<213> Homo sapiens

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552

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180ctatttcaga aagaaagggt atcttttact ggtgagcaca gtcattgctc tgcagatggg  
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360tgaattgtat ttgggtggaac agcaaaaaaa gagaagtatc atttttcttt gtcaaattat  
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626

<210> 710<211> 344<212> DNA<213> Homo sapiens

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120ctccaagatg ttcttgcgcg gggactcagt catcgtggtc ctgcggaacc cgctcatcgc  
180cggcaagtag gggccgctgt ctgttgacag aactcactcc tctgtcctat gaagaccgct  
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344

<210> 711<211> 545<212> DNA<213> Homo sapiens

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180tgtttctaggg cactctggga acctataaag gcaggtatgt cgggccctcc tcttcaggaa  
240tcttcctgaa gacatggccc agtcgaagcc caggatggct tttgctgcgg ccccggtggg  
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420cttattntta ngataactct taangcaact tattcatcct cactttgcct cttacncatg  
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545

<210> 712<211> 503<212> DNA<213> Homo sapiens

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120acaggaagga ggctccttgt gtgccatcag ggagaggcct tggcgccagc tccctaggaa  
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503

<210> 713<211> 443<212> DNA<213> Homo sapiens

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120atttgtagca aatgttcaca aacttattcg ggcgtggtgg tgctgtttg caatcccacc  
180tattggagaa gctggggcgg gagagtctct tgactctaga agacggagggt tgcagtgtc  
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443

<210> 714<211> 364<212> DNA<213> Homo sapiens

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364

<210> 715<211> 173<212> DNA<213> Homo sapiens

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173

<210> 716<211> 431<212> DNA<213> Homo sapiens

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240aacggtagtt ttgtgtgttg gctgctccac tgtcctctgc cagcctacag gaggaaaagc  
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431

<210> 717<211> 220<212> DNA<213> Homo sapiens

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60acatttcatt tggtaacctg tttagaatta taaaatcat ttcatttggc ccagcccata  
120ctgcccaga caaaacttcc agacaattct gatgccatcc agttttgttc ttacaaactg  
180catattaaaa aaaaaaaaaa aaaaaaantt ttcancnccc  
220

<210> 718<211> 332<212> DNA<213> Homo sapiens

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332

<210> 719<211> 520<212> DNA<213> Homo sapiens

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420actgaagtaa gtccctgatgc aggaatgaa tgagtttcac agctttctga cccctcttgc  
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<210> 720<211> 363<212> DNA<213> Homo sapiens

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363

<210> 721<211> 153<212> DNA<213> Homo sapiens

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153



<210> 722<211> 346<212> DNA<213> Homo sapiens

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120tcgatttgag gagtaaaactc aggtttctaa atcacacagt taccatctta ggggtgtgggt  
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346

<210> 723<211> 725<212> DNA<213> Homo sapiens

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725

<210> 724<211> 401<212> DNA<213> Homo sapiens

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<210> 725<211> 371<212> DNA<213> Homo sapiens

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371

<210> 726<211> 360<212> DNA<213> Homo sapiens

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<210> 727<211> 218<212> DNA<213> Homo sapiens

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218

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516

<210> 729<211> 580<212> DNA<213> Homo sapiens

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580

<210> 730<211> 522<212> DNA<213> Homo sapiens

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522

<210> 731<211> 438<212> DNA<213> Homo sapiens

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438

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180agacctgccc gggcgccgc tcgaaagggt gaattccaac nncctgccc cgttactagt  
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282

&lt;210&gt; 733&lt;211&gt; 427&lt;212&gt; DNA&lt;213&gt; Homo sapiens

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420atttccc  
427

&lt;210&gt; 734&lt;211&gt; 458&lt;212&gt; DNA&lt;213&gt; Homo sapiens

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458

&lt;210&gt; 735&lt;211&gt; 509&lt;212&gt; DNA&lt;213&gt; Homo sapiens

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509

&lt;210&gt; 736&lt;211&gt; 445&lt;212&gt; DNA&lt;213&gt; Homo sapiens

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420ncngaacac ccttngggg gaatt  
445

&lt;210&gt; 737&lt;211&gt; 342&lt;212&gt; DNA&lt;213&gt; Homo sapiens

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300ctagtggatc cnanctcggc ccaancttgg ggnaaaanng gg  
342

&lt;210&gt; 738&lt;211&gt; 575&lt;212&gt; DNA&lt;213&gt; Homo sapiens

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420aaacagatgg gcttggtatgt gtttantgta ggtgacangt gcagacaact tcaccaangc  
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575

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499

<210> 740<211> 584<212> DNA<213> Homo sapiens

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<210> 741<211> 206<212> DNA<213> Homo sapiens

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206

<210> 742<211> 476<212> DNA<213> Homo sapiens

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476

<210> 743<211> 398<212> DNA<213> Homo sapiens

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300ccgcgaccac gctaagggcg aattccagca cactggcggc cgttactagt ggatccgagc  
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398

<210> 744<211> 337<212> DNA<213> Homo sapiens  
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120actggtggga ggcggttggg aaagttgcag gaaaacctta gtcttccatc cttctgaccc  
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337

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360agtgggatct aattaaacta aagagcttct tgcncagcaa aagaaaccac catcagagaa  
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<210> 746<211> 169<212> DNA<213> Homo sapiens  
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169

<210> 747<211> 352<212> DNA<213> Homo sapiens  
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352

<210> 748<211> 319<212> DNA<213> Homo sapiens  
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319

<210> 749<211> 595<212> DNA<213> Homo sapiens  
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595

<210> 750<211> 379<212> DNA<213> Homo sapiens

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240gggaaagggtg aaaagaggaa naanaaaacc nmatnattga agggagaaan atgatttaan  
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204

<210> 753<211> 422<212> DNA<213> Homo sapiens

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422

<210> 754<211> 365<212> DNA<213> Homo sapiens

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365

<210> 755<211> 343<212> DNA<213> Homo sapiens

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120tctagaaata tacatagaca aagtttagcta atgaataaaa taagtaaaat gactacataa  
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 343

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 327

<210> 758<211> 535<212> DNA<213> Homo sapiens  
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 535

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 278

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608

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365

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384

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297

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480cgtactagt gatccnactc ggaccaactt ggcgtaatat ggcatacttt ttctgtga  
539

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180agaatcactt catttacctc ggccgcgacc acgctaaggg cgaattccag cacactggcg  
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309

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498

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223

&lt;210&gt; 773&lt;211&gt; 448&lt;212&gt; DNA&lt;213&gt; Homo sapiens

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448

&lt;210&gt; 774&lt;211&gt; 253&lt;212&gt; DNA&lt;213&gt; Homo sapiens

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93

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439

&lt;210&gt; 777&lt;211&gt; 315&lt;212&gt; DNA&lt;213&gt; Homo sapiens

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315

&lt;210&gt; 778&lt;211&gt; 392&lt;212&gt; DNA&lt;213&gt; Homo sapiens

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392

&lt;210&gt; 779&lt;211&gt; 443&lt;212&gt; DNA&lt;213&gt; Homo sapiens

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289

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471

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695

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386

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300taataaatat gtaatatataa tttaagcaaa cgtctatttt gtatatttgt aaactacaaa

360gtaaaatgaa cattttgttg agtttgtatt ttgcatactc aaggngagaa tttaagtttt  
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517

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188

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600a  
601

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240ggcttaattt acatgtagtg ccaggactg ttcaatgcgc ctgcaattaa accaaggacc  
300tcggccgcga ccacgctaag ggcaattcc agcacttg cgcccgctt tagtggatcc  
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404

<210> 804<211> 101<212> DNA<213> Homo sapiens  
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101

<210> 805<211> 514<212> DNA<213> Homo sapiens  
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360ctttgcttgt cctctttgcc ttcggttaata tgtataaact tacatcacga ctttctntta  
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514

<210> 806<211> 367<212> DNA<213> Homo sapiens  
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367

<210> 807<211> 451<212> DNA<213> Homo sapiens

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120gtgaagtcag tcaagtgaag gagacttttg aaaaagaact tcagattttg aaagaaaagt  
180ttgctgaagc ttcagaggag gcagtctctg ttcagagaag tatgcaagaa actgtaaata  
240agttacacca aaaggaggaa cagttaaca tgctgtcttc tgacttggag aagctgagag  
300aaaacttagc agatatggag gcaaaattta gagagaaaga tgagagagaa gagcagacct  
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451

<210> 808<211> 502<212> DNA<213> Homo sapiens

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120ctcaacaaat gtttttagtga atgaatgaat gattgactaa agaaaaacat gagttactta  
180gtgaccaaat ctaatactca gtggaatagc tgattataat cgctaaaata ttcataatag  
240aaataaagag atctgtatgc agtctactcc atatagtcaa aagatctcat ggtagccttt  
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360gtgacttctt agggagatgt tttangaaaa attattaata cctcggnccgc gaccacgcta  
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502

<210> 809<211> 502<212> DNA<213> Homo sapiens

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120aagaagggtc tgttctgttg ctgagctagg tgaaccccg gtaggggaa agatgttaac  
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502

<210> 810<211> 443<212> DNA<213> Homo sapiens

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120aaggcagttc cgtaagggt ttttgttttt aaactttttt ttgccatcca tctgtgcaa  
180tatgccgtgt agaataattt tcttaaaatt caaggccaca aaaacaatgt ttgggggaaa  
240aaaaagaaag aatcatgcca gctaatacat tcaagttcac tgcctgtcag attgttgata  
300tataccttct gtaaataact ttttttgaga aggaaataaa atcagacctg cccggggcgc  
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443

<210> 811<211> 675<212> DNA<213> Homo sapiens

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120taccatgtg tacagcctac ccattgcagg actgggattc gaggacttcc aggcgcatag  
180ggtaggacca aatgataggg taggagcatg tgttctttag ggccttgtaa ggctgtttcc  
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420tgaattgtgt ttgttttttc ctttgatgga cttaaaagaa attattcaaa gggaaaaaaa  
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540aatccaaagg gtntttttgn agnatgcttg acttttccca tttttnanga catctttccg  
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675

<210> 812<211> 448<212> DNA<213> Homo sapiens  
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448

<210> 813<211> 372<212> DNA<213> Homo sapiens  
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120aaataacact tagaagggtg tgtattttta gttagggttt ctgtatcttg gaggatgttt  
180gaaagttaaa aattgaattt ggtaaccaa ggactgattt atgggtcttt cctatcttaa  
240ccaacgtttt cttagttacc tagatggacc tgcccgggc gccgctaagg gcgaattcca  
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372

<210> 814<211> 603<212> DNA<213> Homo sapiens  
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480caatatgang caatagtatt ttactggacc tcggccgcga acaccttang gcgaaatcna  
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600ggg  
603

<210> 815<211> 371<212> DNA<213> Homo sapiens  
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60aatagacacc agtggggcgg tcaccacaca gtacctgaaa aatacagcta aaaaaggagg  
120agtctgttga gtatttaatt tcagatctac ttgactcctt gttgaacggc ttaagttag  
180catatagtga gtgagaggta gagtcccaag tataatagct gatgcctcag ggctccattt  
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371

<210> 816<211> 449<212> DNA<213> Homo sapiens  
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120gtttttgtgg ccttgaattt taagacaaat attctacacg gcatattgca caggatggat  
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449

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298

<210> 818<211> 326<212> DNA<213> Homo sapiens  
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180tcaggccctg cagggcccta tagaacctgt ggacctgcc gggcgccgc tcgaaagggc  
240gaattccagc acacttgccg ccgttactag tggatccnag ctcggtacca agcttggcgt  
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326

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240anctnaccat cactgttgg gtccagttc ttcatcatgc ggcaaggaca ccagggtcct  
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450

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519

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360tanagaacac atccatagtc tggactttag agcagcttan aggcanaagt tcttnagtca  
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564

<210> 822<211> 373<212> DNA<213> Homo sapiens

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373

<210> 823<211> 577<212> DNA<213> Homo sapiens

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577

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390

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120ccttttacttg atggtttagag ttctgtcatt tatgaaatca aatctgtaat aacagaaatc  
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364

<210> 826<211> 219<212> DNA<213> Homo sapiens

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120cgccgctcg aagggcgaat tccagcacac tgcggccgtt actagtggat ccgagctcgg  
180taccaagctt ggcgtaata tggatcatag tgttttccg  
219

<210> 827<211> 261<212> DNA<213> Homo sapiens

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261

<210> 828<211> 388<212> DNA<213> Homo sapiens

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120caagccatgg gtagcctggg tgtaaaacct ggagatggtg gatgatcccc acgccacagc  
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345

<210> 830<211> 319<212> DNA<213> Homo sapiens

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240cggcgcccg ctcaaggcg aattccagca cactggcggc cgttactagt ggatccgagc  
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343

<210> 833<211> 378<212> DNA<213> Homo sapiens

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378

<210> 834<211> 533<212> DNA<213> Homo sapiens

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533

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438

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193

<210> 837<211> 324<212> DNA<213> Homo sapiens

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324

<210> 838<211> 268<212> DNA<213> Homo sapiens

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268

<210> 839<211> 498<212> DNA<213> Homo sapiens

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498

&lt;210&gt; 840&lt;211&gt; 470&lt;212&gt; DNA&lt;213&gt; Homo sapiens

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470

&lt;210&gt; 841&lt;211&gt; 378&lt;212&gt; DNA&lt;213&gt; Homo sapiens

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378

&lt;210&gt; 842&lt;211&gt; 552&lt;212&gt; DNA&lt;213&gt; Homo sapiens

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552

&lt;210&gt; 843&lt;211&gt; 569&lt;212&gt; DNA&lt;213&gt; Homo sapiens

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569

&lt;210&gt; 844&lt;211&gt; 501&lt;212&gt; DNA&lt;213&gt; Homo sapiens

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195

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74

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336

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283

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148

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455

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180gtttaatcat cgggtggcag gatttctttg aagtagaatc tggtagtacc cctcccaatc  
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506

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288

<210> 868<211> 243<212> DNA<213> Homo sapiens  
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120gatgtatata cctcgccgc gaccacgcta agggcgaatt ccagcacact ggcggccgtt  
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373

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352

<210> 872<211> 390<212> DNA<213> Homo sapiens  
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390

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120ggagcttctg ctacagacc attttattct cactctcca tttcaccagg ctcttacagg  
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378

<210> 875<211> 325<212> DNA<213> Homo sapiens  
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325

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<210> 877<211> 225<212> DNA<213> Homo sapiens

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 120tacgagtaac tngaattctg tgtaatagcc tacatctcac agaccatcag ggatgagnna  
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<210> 882<211> 382<212> DNA<213> Homo sapiens

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 320

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<210> 890<211> 627<212> DNA<213> Homo sapiens

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<210> 923<211> 239<212> DNA<213> Homo sapiens

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<210> 924<211> 240<212> DNA<213> Homo sapiens

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 120agggatggga aggaaggagc ccttaccccc ggctcttctc ctgacctgcc aataaaaatt  
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 120aacaactccc ctgacacatc taggaggact cttggctctt cagacacaca gcaactcaga  
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<210> 926<211> 517<212> DNA<213> Homo sapiens

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 300ctctgcaaaa actgtactgt cttgtttctg cattagactt aagtagtcat gtgaatatac  
 360tgctatgtca cttttaatat taogagtttt atacttggaa aatgggtactt gcttctttta  
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 120tggtgctgac caggaattct ttgtggacat tggcccagtc tgtttcaaataaatgaactc  
 180aatctaaatt aaaaagaaag aaatttgaaa aaactttctc tttgccattt ctctctcttc  
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 480ttgtggcttt tgaatatatt cacagaggaa attacctgcc cggcggcctc caaaggcgaa  
 540ttcacacctg nggcctntan ggaccacttg nnccacttgg gnaatatggc ta  
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 120cctacatgaa aaancagttt gccaaagttt agtctcaaaa aatgactggg tggctntatt  
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 120aagggcggaat tccagcacac tgnngccgtt actagtggat ccgagctcgg taccaagctt  
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 212

<210> 934<211> 98<212> DNA<213> Homo sapiens  
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98

<210> 935<211> 582<212> DNA<213> Homo sapiens  
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 300cacttaagtc ttccttaaat gacttttctt aagtaatgat actgtgtgtt ttcccaaagc  
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 420ttctanaatt tttttcttac caaaatttcc ctaatctttg aaagggtttg ggaaatttaa  
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<210> 937<211> 359<212> DNA<213> Homo sapiens

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240tcaaattttt tacctgcccg ggcggccgct cgaaggcg aattccagca cactggcggc  
300cgttactagt ggatccgact cggtagcaag cttggcgtaa tcatggcata gctgtttcc  
359

<210> 938<211> 153<212> DNA<213> Homo sapiens

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120aacatttggt caaaaaaaaa aaaaaaaaaa aaa  
153

<210> 939<211> 274<212> DNA<213> Homo sapiens

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120ccttcttggt tcaaacttaa aaaaaagcag aggaagaggg gagggaccac ttcaaacaaa  
180gtttaaaaaa tctttcagag taattgccaa cataaccttt catgttggac ctcgcccgcg  
240accacgctaa gggcgaattc cagcacactg gcgg  
274

<210> 940<211> 696<212> DNA<213> Homo sapiens

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696

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321

<210> 942<211> 575<212> DNA<213> Homo sapiens

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120ctaggtatga tactgccaac taaaacatac tgtaaagcat gagttatact ctataacaaa  
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420taatttgggt gtatgtgngn ctgctacctg acccccatgg aacaacttat atntttataa  
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575

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 360gtgtcttaaa attccaaaca aaatgatccc tgcatttctg aagatgttta cctcggccgc  
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 499

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<210> 951<211> 506<212> DNA<213> Homo sapiens

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<210> 953<211> 379<212> DNA<213> Homo sapiens

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<210> 954<211> 608<212> DNA<213> Homo sapiens

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 608

<210> 955<211> 201<212> DNA<213> Homo sapiens

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<210> 957<211> 693<212> DNA<213> Homo sapiens

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<210> 958<211> 593<212> DNA<213> Homo sapiens

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 120aagccagcct catacatgcc ctgaggccag caggcgccca gtcaggcag cacacgcctt  
 180cacttaaaaa ggccgaggag cggcgggatc cactgaatc caattacatc tggtagaactc  
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 120agaccctgtg ctttcatgaa agtgaaaatc tggctgaacc agttccaca gggtactgta  
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 120tttagatccc tattccaca ctctaataag ctgtataatt tttgtttaga atttttctgc  
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 240aatatcaca cattacatt ttatcttaaa ggacaagcaa actttcaggg ttgataatgg  
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274

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311

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318

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<210> 967<211> 402<212> DNA<213> Homo sapiens  
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402

<210> 968<211> 425<212> DNA<213> Homo sapiens  
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425

<210> 969<211> 298<212> DNA<213> Homo sapiens  
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298

&lt;210&gt; 970&lt;211&gt; 526&lt;212&gt; DNA&lt;213&gt; Homo sapiens

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 526

&lt;210&gt; 971&lt;211&gt; 449&lt;212&gt; DNA&lt;213&gt; Homo sapiens

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 449

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 300g  
 301

&lt;210&gt; 973&lt;211&gt; 570&lt;212&gt; DNA&lt;213&gt; Homo sapiens

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 570

&lt;210&gt; 974&lt;211&gt; 616&lt;212&gt; DNA&lt;213&gt; Homo sapiens

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616

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532

<210> 976<211> 404<212> DNA<213> Homo sapiens

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404

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<210> 978<211> 508<212> DNA<213> Homo sapiens

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508

<210> 979<211> 444<212> DNA<213> Homo sapiens

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<210> 980<211> 447<212> DNA<213> Homo sapiens

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120acaggtacag cagcgctttc tggtagtcgc ccttagtgctc ttgctggata aacgtca  
180taaataacaa aaaacaaagt aggtcccaga ctccggacca tgcancanga acagggtg  
240gaagggttgt tgaatgggaa aaggtggaag ggggctacac catcacctaa aaacagtcac  
300cagaaaaaga atgggctttc aagggaacact tgcccctttc cttgaccttc gggccgcgaa  
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447

<210> 981<211> 720<212> DNA<213> Homo sapiens

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120tgatataaaa tatgttgtct tttgtttaag catctatttt caaacactaa ggagcttttt  
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540cttgactggg ggnaaaaaaa angggtgcat ggnttcctaa nttgggataa tgggttccca  
600ntttttggga aaanaagaat taaataaaac ttttttacct cggnccnnaa caccctaag  
660ggngaaattc cacacacttt gggggcggtt taatggaacc aacttngtnc caacttgggg  
720

<210> 982<211> 459<212> DNA<213> Homo sapiens

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240tgttatgcag gactttcccg ttaaaaaaaa aaaaaatcga aatattttta ctcaagtaag  
300tttaattccc ncagaggagc ttaaaaaaaa aanagggggg tagtaaaatc canntacttt  
360ttttcctngg gcgnnaccac nctaanggcg aattccacac acttggcggc cgttactaat  
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459

<210> 983<211> 327<212> DNA<213> Homo sapiens

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120taatagtatt tcagataact gaagaatggt gatgggtgta gaagaatttg agaagaaata  
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327

<210> 984<211> 200<212> DNA<213> Homo sapiens

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200

<210> 985<211> 223<212> DNA<213> Homo sapiens

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120cggcgctcg aaaggcgaa attccagcac actgcgggcc gttctagtgg atccgagctc  
180ggtaccaagc ttggcgtaat catggcatac ttggttcctg gaa

223

&lt;210&gt; 986&lt;211&gt; 189&lt;212&gt; DNA&lt;213&gt; Homo sapiens

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 120gtagaactaa ggcttctgct tccttgctgc ttgggggtggg agtagggaaa tgttatgatt  
 180tgatttaca  
 189

&lt;210&gt; 987&lt;211&gt; 340&lt;212&gt; DNA&lt;213&gt; Homo sapiens

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 240acgctaangg cgaaattcaa cacacttgcg ggccgtacta ntggaatccn anctcgggac  
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 340

&lt;210&gt; 988&lt;211&gt; 286&lt;212&gt; DNA&lt;213&gt; Homo sapiens

cggggcaggt ctatagggtc cgagcggccg cccgggcagg tccaagcttg aggaagatgt  
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 120attttaggggc tggggagggg gaaggggcaa gaacttggac cttgtactac ctcaagacct  
 180cggggccgcga acacgcttaa gggcgaattt cancacactt gcggccgtac tagtggatcc  
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 286

&lt;210&gt; 989&lt;211&gt; 488&lt;212&gt; DNA&lt;213&gt; Homo sapiens

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 240aaatttagtgg gcagaaacat catacaccca ttctcctnaa cccatttttc gggctggtag  
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 420cacactgngc ggccggtctt agnggatccc aactcgttac caacntggcg taatatgggc  
 480atactggt  
 488

&lt;210&gt; 990&lt;211&gt; 478&lt;212&gt; DNA&lt;213&gt; Homo sapiens

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 420tcnggtaccc aangcntttg ggcgtaaaat tcattngggn caataaacct tgtttntt  
 478

&lt;210&gt; 991&lt;211&gt; 378&lt;212&gt; DNA&lt;213&gt; Homo sapiens

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 120caaaataggc tgaaagaaaa aaagcaatcc tctgagttct aggtttcaca aaaggaccac  
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 378



<210> 992<211> 581<212> DNA<213> Homo sapiens

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120tgctataatg tactgaaacc accatattac agaaatattt actacatatt ttccatctgt  
180agttttctcag aagggtatg gattaagttt gaactgtcaa atccttgcat acttctgtga  
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300gtatgttttc cagtaaaacta gaagtatgat atttgataat tatatttgn tttcaccacc  
360taaatgtaat ggtgatttct caagaatgaa atgaangcac tacattgaaa tatggtttgn  
420ataaatttgn catggtgaac aacattttta catgggaagg tnccttacta tatgaatttt  
480ggcatggttc aaanaaacia taaataaaac ctgccccggc ggcgccaag gcgaattcca  
540cnacttgagg cgntcaatgg accactcgnc cacttgggaa c  
581

<210> 993<211> 389<212> DNA<213> Homo sapiens

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389

<210> 994<211> 542<212> DNA<213> Homo sapiens

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120atctgnaaga aagaaggagc aacttttggg caaataatct gctacccttt taattgggaa  
180ataagaatgg gaaaatatga atgcttaatc aaatttttta aaaaatcccc nccccgatcc  
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542

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120tatccagtg tgtgtttaac attcacagcc caaaaccag atgtgtcttg gaaaaccttg  
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488

<210> 996<211> 379<212> DNA<213> Homo sapiens

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379

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 420aatggagaaa accttgcanc tcttgatgt acttgatggg ttacagtaaa nactgaacag  
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<210> 999<211> 361<212> DNA<213> Homo sapiens

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<210> 1001<211> 441<212> DNA<213> Homo sapiens

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<210> 1002<211> 480<212> DNA<213> Homo sapiens

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480

<210> 1003<211> 297<212> DNA<213> Homo sapiens

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120tcaggattac atactgtgtc ggaattgatg gtttcttggg ctactgact tcaagaaaga  
180agcacctgcc cgggcgcgcg tcaaaggcg aaattccagc acacttgagg gccgttctag  
240tggatccgag cttcgttacc caagctttgc gtaatcatgg tcatanctgt ttttctg  
297

<210> 1004<211> 548<212> DNA<213> Homo sapiens

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420taattaagggt attttagggg aaacttccca cccnttttaa aaaataaaaag gtcccantct  
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548

<210> 1005<211> 218<212> DNA<213> Homo sapiens

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120tttaccatct ctactgccc ggcggcgtc gaaggcaatt cacacacttg cggcgtctat  
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218

<210> 1006<211> 215<212> DNA<213> Homo sapiens

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215

<210> 1007<211> 340<212> DNA<213> Homo sapiens

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340

<210> 1008<211> 256<212> DNA<213> Homo sapiens

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<210> 1016<211> 371<212> DNA<213> Homo sapiens

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<210> 1017<211> 287<212> DNA<213> Homo sapiens

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<210> 1039<211> 304<212> DNA<213> Homo sapiens

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304

<210> 1040<211> 495<212> DNA<213> Homo sapiens

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<210> 1041<211> 472<212> DNA<213> Homo sapiens

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 180ctctgcactg ttgctcagga ctgagaagac actggaggag ccagccccgg ggtactcact  
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<210> 1042<211> 622<212> DNA<213> Homo sapiens

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 240ctgggctttg tcctgggaat atggtaggtt ggtgatggtg aaattcaggt agaagtgctg  
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 420gacttgctcc accangcttg gggccaaat tggaggagaa caatgncttg acaagtgacc  
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<210> 1043<211> 255<212> DNA<213> Homo sapiens

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<210> 1044<211> 444<212> DNA<213> Homo sapiens

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<210> 1045<211> 397<212> DNA<213> Homo sapiens

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<210> 1048<211> 363<212> DNA<213> Homo sapiens  
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<210> 1049<211> 297<212> DNA<213> Homo sapiens  
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<210> 1050<211> 378<212> DNA<213> Homo sapiens  
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<210> 1053<211> 627<212> DNA<213> Homo sapiens

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<210> 1055<211> 508<212> DNA<213> Homo sapiens

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325

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660

<210> 1059<211> 580<212> DNA<213> Homo sapiens

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580

<210> 1060<211> 271<212> DNA<213> Homo sapiens

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271

<210> 1061<211> 455<212> DNA<213> Homo sapiens

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325

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352

<210> 1064<211> 378<212> DNA<213> Homo sapiens

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378

<210> 1065<211> 281<212> DNA<213> Homo sapiens

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<210> 1069<211> 211<212> DNA<213> Homo sapiens  
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 240tttgaaacat gtttttattt gcaatatatg cctgactgaa ttaagctngc ttggtttaaa  
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539

&lt;210&gt; 1074&lt;211&gt; 442&lt;212&gt; DNA&lt;213&gt; Homo sapiens

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 442

&lt;210&gt; 1075&lt;211&gt; 498&lt;212&gt; DNA&lt;213&gt; Homo sapiens

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 498

&lt;210&gt; 1076&lt;211&gt; 453&lt;212&gt; DNA&lt;213&gt; Homo sapiens

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 453

&lt;210&gt; 1077&lt;211&gt; 581&lt;212&gt; DNA&lt;213&gt; Homo sapiens

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 540ttaaggcgaa ttcncccc tnnccgcntt cctatgganc c  
 581

&lt;210&gt; 1078&lt;211&gt; 413&lt;212&gt; DNA&lt;213&gt; Homo sapiens

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 60ctgacagctc tttagcagat atgttttttt cattttttac ctggccgcg accacgctaa  
 120gggcgaattc cagcacactg gcggccgtta ctagtggatc cgagctcggg accaagcttg  
 180gcgtaatcat ggtcatagct gtttcccggg a  
 211

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396

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385

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413

&lt;210&gt; 1110&lt;211&gt; 247&lt;212&gt; DNA&lt;213&gt; Homo sapiens

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 240catagct  
 247

&lt;210&gt; 1111&lt;211&gt; 207&lt;212&gt; DNA&lt;213&gt; Homo sapiens

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 207

&lt;210&gt; 1112&lt;211&gt; 560&lt;212&gt; DNA&lt;213&gt; Homo sapiens

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 560

&lt;210&gt; 1113&lt;211&gt; 395&lt;212&gt; DNA&lt;213&gt; Homo sapiens

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 395

&lt;210&gt; 1114&lt;211&gt; 605&lt;212&gt; DNA&lt;213&gt; Homo sapiens

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 605

&lt;210&gt; 1115&lt;211&gt; 695&lt;212&gt; DNA&lt;213&gt; Homo sapiens

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<210> 1117<211> 702<212> DNA<213> Homo sapiens

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300cgtaatcatg ggncatagct ggttncctgt g  
331

<210> 1121<211> 524<212> DNA<213> Homo sapiens

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<210> 1131<211> 720<212> DNA<213> Homo sapiens

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 600caaaaaccg naaaaaaann aattggaaat aaacttttnc ccttgnaatn ttttttncaa  
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<210> 1132<211> 633<212> DNA<213> Homo sapiens

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<210> 1133<211> 468<212> DNA<213> Homo sapiens

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<210> 1134<211> 213<212> DNA<213> Homo sapiens

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 213

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488

&lt;210&gt; 1136&lt;211&gt; 316&lt;212&gt; DNA&lt;213&gt; Homo sapiens

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 316

&lt;210&gt; 1137&lt;211&gt; 528&lt;212&gt; DNA&lt;213&gt; Homo sapiens

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 528

&lt;210&gt; 1138&lt;211&gt; 418&lt;212&gt; DNA&lt;213&gt; Homo sapiens

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 418

&lt;210&gt; 1139&lt;211&gt; 390&lt;212&gt; DNA&lt;213&gt; Homo sapiens

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 390

&lt;210&gt; 1140&lt;211&gt; 456&lt;212&gt; DNA&lt;213&gt; Homo sapiens

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 456

&lt;210&gt; 1141&lt;211&gt; 498&lt;212&gt; DNA&lt;213&gt; Homo sapiens

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<210> 1144<211> 620<212> DNA<213> Homo sapiens

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 173

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120aaggagaaac ccacttgga ctcggccgcg accacgctaa gggcgaattc cagcacactg  
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248

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300aaaaggttgg aagttgcaca cctcgccgc gaccacgcta agggcgaatt ccacacactg  
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 120aaaagaattt ttttTgtctt acctcggccg cgaccacgct aagggcgaat tccagcacac  
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 180aactaaagtt tttattttta cattgtgatt ttacattaa aatattaact tttttaatg  
 240ctattttatg aaagattatt gtaataaact ttgatgggtt ttgtattttg gttaatcttc  
 300atgaattgaa taattgtttt tttaaagcaa aataaagttt tttaaataaa tggaaaaaaa  
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<210> 1158<211> 272<212> DNA<213> Homo sapiens

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<210> 1159<211> 392<212> DNA<213> Homo sapiens

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<210> 1160<211> 587<212> DNA<213> Homo sapiens

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<210> 1161<211> 479<212> DNA<213> Homo sapiens

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<210> 1162<211> 427<212> DNA<213> Homo sapiens

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<210> 1163<211> 412<212> DNA<213> Homo sapiens



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<210> 1164<211> 419<212> DNA<213> Homo sapiens

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<210> 1165<211> 422<212> DNA<213> Homo sapiens

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<210> 1167<211> 579<212> DNA<213> Homo sapiens

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<210> 1168<211> 440<212> DNA<213> Homo sapiens

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255

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213

<210> 1250<211> 407<212> DNA<213> Homo sapiens

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407

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<210> 1252<211> 418<212> DNA<213> Homo sapiens

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<210> 1253<211> 425<212> DNA<213> Homo sapiens

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120gcagggcctc cccagccca cgttaggaa tgcttggcct ctggcaggca ggcagacctg  
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289

<210> 1274<211> 404<212> DNA<213> Homo sapiens

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240agtccagtg gcacatcttg aggtcacggc aggtgcgggc ggggttcttg cactcggcc  
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<210> 1275<211> 284<212> DNA<213> Homo sapiens

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284

<210> 1276<211> 407<212> DNA<213> Homo sapiens

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407

<210> 1277<211> 263<212> DNA<213> Homo sapiens

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120gcaagtatct atatatcac aaaagaattc cttttcttaa aaaaaaaaaa aaanggnnc  
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263

<210> 1278<211> 272<212> DNA<213> Homo sapiens

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272

<210> 1279<211> 738<212> DNA<213> Homo sapiens

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 738

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 220

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<210> 1285<211> 279<212> DNA<213> Homo sapiens  
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180atttttttaa tntncaata aaaagtttac ctgccgggc ggccgntcaa gggcaaatc  
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279

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335

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311

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440

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714

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459

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<210> 1302<211> 87<212> DNA<213> Homo sapiens

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<210> 1304<211> 729<212> DNA<213> Homo sapiens

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 300acgacaagag tgagcattcc cgccagtaaa tcttcaaggg tggcatccgt ttcaatttat  
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660ccccagtggg gtttcgngca acccnttcct tccanaaact ggtgtaaggg gggaaatttg  
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<210> 1306<211> 496<212> DNA<213> Homo sapiens

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<210> 1307<211> 680<212> DNA<213> Homo sapiens

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<210> 1308<211> 283<212> DNA<213> Homo sapiens

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<210> 1309<211> 428<212> DNA<213> Homo sapiens

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<210> 1311<211> 464<212> DNA<213> Homo sapiens

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464

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<210> 1313<211> 523<212> DNA<213> Homo sapiens

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<210> 1314<211> 531<212> DNA<213> Homo sapiens

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90

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 120ctgcttgctt ctctgttca acctgcccgg ccggccgctc aagggcgaat tccagcacac  
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347

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508

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<210> 1339<211> 331<212> DNA<213> Homo sapiens

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 180aggatggatt tggctggctg gagtcacatc ttggggaagc tggacctgcc cgggcggccg  
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<210> 1340<211> 447<212> DNA<213> Homo sapiens  
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 420catctcacc atctccttta cctcgccgc gaccacgcta anggcgaatt ccagcacact  
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575

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<210> 1368<211> 668<212> DNA<213> Homo sapiens

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<210> 1370<211> 143<212> DNA<213> Homo sapiens

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<210> 1371<211> 476<212> DNA<213> Homo sapiens

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 398

<210> 1375<211> 568<212> DNA<213> Homo sapiens

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660

<210> 1415<211> 448<212> DNA<213> Homo sapiens

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<210> 1416<211> 496<212> DNA<213> Homo sapiens

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496

<210> 1417<211> 228<212> DNA<213> Homo sapiens

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120ggggattgaa aaaaattggg ggggtataatc ttctgattca caattcccag ccacattctt  
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228

<210> 1418<211> 375<212> DNA<213> Homo sapiens

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375

<210> 1419<211> 292<212> DNA<213> Homo sapiens

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120gctccaggga gcttggcttc tgtagaagtt ctaaggaagc ggtacgaact ccacggcgga  
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292

<210> 1420<211> 435<212> DNA<213> Homo sapiens

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<210> 1421<211> 741<212> DNA<213> Homo sapiens

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741

<210> 1422<211> 349<212> DNA<213> Homo sapiens

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349

<210> 1423<211> 391<212> DNA<213> Homo sapiens

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180ggggaatat ttactgtcgt cttttccctt cccagggtga ttactgacct gtttgttggtg  
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<210> 1424<211> 440<212> DNA<213> Homo sapiens  
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 180cagacagtac agtcccactg acataacatt tagtatgatg tcctactctc atattagaat  
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<210> 1426<211> 625<212> DNA<213> Homo sapiens  
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120attcttttata ccattcacaa ttccccttgt atagccatga tgccatttat gcacttcagc  
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 448

<210> 1429<211> 346<212> DNA<213> Homo sapiens

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 346

<210> 1430<211> 346<212> DNA<213> Homo sapiens

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 180atttgggaata ttgttgtggt cttttgtttt ttctcttagt atagcatttt tacctgcccg  
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<210> 1431<211> 315<212> DNA<213> Homo sapiens

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 180aaaacactta ctaccaacac agacctcggc cgcgaccacg ctaagggcga attccagcac  
 240actggcgcc gttactagt gatccgagct cggtagcaag cttggcgtaa tcatggtcat  
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 315

<210> 1432<211> 563<212> DNA<213> Homo sapiens

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381

<210> 1440<211> 601<212> DNA<213> Homo sapiens

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<210> 1442<211> 449<212> DNA<213> Homo sapiens

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<210> 1443<211> 404<212> DNA<213> Homo sapiens

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180atcttcacct cagagtggag ttgaaactgc tatagcctaa gcggctgtt actgcttttc  
240attagcagtt gctcacatgt ctttgggtgg gggggagaag aagaattgga cctgcccggg  
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 120atttcagct cctgttctct ggaaaatctc cattgtatgt gcatttttta cctcgccgcg  
 180gaccacgcta agggcgaatt ccagcacact ggcgccggtt actagtggat ccgagctcgg  
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<210> 1448<211> 729<212> DNA<213> Homo sapiens  
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<210> 1449<211> 498<212> DNA<213> Homo sapiens

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<210> 1450<211> 285<212> DNA<213> Homo sapiens  
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<210> 1451<211> 285<212> DNA<213> Homo sapiens  
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 180cgcgaccacg ctaaggcgga attccagcac actggcgccc gttactagtg gatccgagct  
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<210> 1452<211> 275<212> DNA<213> Homo sapiens  
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 275

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<210> 1454<211> 201<212> DNA<213> Homo sapiens  
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 201

<210> 1455<211> 292<212> DNA<213> Homo sapiens  
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 292

<210> 1456<211> 711<212> DNA<213> Homo sapiens  
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<210> 1457<211> 682<212> DNA<213> Homo sapiens

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<210> 1458<211> 581<212> DNA<213> Homo sapiens

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<210> 1459<211> 504<212> DNA<213> Homo sapiens

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<210> 1460<211> 392<212> DNA<213> Homo sapiens

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392

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<210> 1462<211> 291<212> DNA<213> Homo sapiens

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291

<210> 1463<211> 279<212> DNA<213> Homo sapiens

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279

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370

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223

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623

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<210> 1471<211> 470<212> DNA<213> Homo sapiens



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 240gcaaatccc ttaatttatg tgcaccgttg ggaccaatgc cttaattaaa gaatttaaaa  
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<210> 1473<211> 585<212> DNA<213> Homo sapiens  
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 180ccaggcccca cctgtcttgt cactgtcgt tctgtctggt ctctgtcact gatgtgata  
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 120agtgtatttt atagaattga agttaacatt cttattttca agagaattta tggacgttgt  
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<210> 1477<211> 289<212> DNA<213> Homo sapiens

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<210> 1478<211> 575<212> DNA<213> Homo sapiens

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<210> 1479<211> 495<212> DNA<213> Homo sapiens

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<210> 1480<211> 492<212> DNA<213> Homo sapiens

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<210> 1481<211> 427<212> DNA<213> Homo sapiens

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427

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<210> 1483<211> 568<212> DNA<213> Homo sapiens  
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568

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527

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319

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<210> 1488<211> 263<212> DNA<213> Homo sapiens

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<210> 1489<211> 654<212> DNA<213> Homo sapiens

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121

<210> 1492<211> 502<212> DNA<213> Homo sapiens

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326